B126

(54) Title: EXTRACELLULAR MATRIX AND CELL ADHESION MOLECULES

(57) Abstract: The invention provides human extracellular matrix and cell adhesion molecules (XMAD) and polynucleotides which identify and encode XMAD. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associates with expression of XMAD.

EXTRACELLULAR MATRIX AND CELL ADHESION MOLECULES

TECHNICAL FIELD

This invention relates to nucleic acid and amino acid sequences of extracellular matrix and cell

5   adhesion molecules and to the use of these sequences in the diagnosis, treatment, and prevention of

genetic, autoimmune/inflammation, and cell proliferative disorders, including cancer, and in the

assessment of the effects of exogenous compounds on the expression of nucleic acid and amino acid

sequences of extracellular matrix and cell adhesion molecules.

BACKGROUND OF THE INVENTION

10

Extracellular Matrix Proteins

The extracellular matrix (ECM) is a complex network of glycoproteins, polysaccharides,

proteoglycans, and other macromolecules that are secreted from the cell into the extracellular space.

The ECM remains in close association with the cell surface and provides a supportive meshwork that

15   profoundly influences cell shape, motility, strength, flexibility, and adhesion. In fact, adhesion of a cell

to its surrounding matrix is required for cell survival except in the case of metastatic tumor cells, which

have overcome the need for cell-ECM anchorage. This phenomenon suggests that the ECM plays a

critical role in the molecular mechanisms of growth control and metastasis. (Reviewed in Ruoslahti, E.

(1996) Sci. Am. 275:72-77.) Furthermore, the ECM determines the structure and physical properties

20   of connective tissue and is particularly important for morphogenesis and other processes associated

with embryonic development and pattern formation.

The collagens comprise a family of ECM proteins that provide structure to bone, teeth, skin,

ligaments, tendons, cartilage, blood vessels, and basement membranes. Multiple collagen proteins have

been identified. Three collagen molecules fold together in a triple helix stabilized by interchain disulfide

25   bonds. Bundles of these triple helices then associate to form fibrils.

Elastin and related proteins confer elasticity to tissues such as skin, blood vessels, and lungs.

Elastin is a highly hydrophobic protein of about 750 amino acids that is rich in proline and glycine

residues. Elastin molecules are highly cross-linked, forming an extensive extracellular network of fibers

and sheets. Elastin fibers are surrounded by a sheath of microfibrils which are composed of a number

30   of glycoproteins, including fibrillin.

Fibronectin is a large ECM glycoprotein found in all vertebrates. Fibronectin exists as a dimer

of two subunits, each containing about 2,500 amino acids. Each subunit folds into a rod-like structure

containing multiple domains. The domains each contain multiple repeated modules, the most common

of which is the type III fibronectin repeat. The type III fibronectin repeat is about 90 amino acids in

length and is also found in other ECM proteins and in some plasma membrane and cytoplasmic proteins. Furthermore, some type III fibronectin repeats contain a characteristic tripeptide consisting of Arginine-Glycine-Aspartic acid (RGD). The RGD sequence is recognized by the integrin family of cell surface receptors and is also found in other ECM proteins. (Reviewed in Alberts, supra, pp. 986-987.)

5   Laminin is a major glycoprotein component of the basal lamina which underlies and supports epithelial cell sheets. Laminin is one of the first ECM proteins synthesized in the developing embryo. Laminin is an 850 kilodalton protein composed of three polypeptide chains joined in the shape of a cross by disulfide bonds. Laminin is especially important for angiogenesis and, in particular, for guiding the formation of capillaries.   (Reviewed in Alberts, B., et al. (1994) Molecular Biology of the

10   Cell, Garland Publishing, New York, NY, pp. 990-991.)

Many proteinaceous ECM components are proteoglycans. Proteoglycans are composed of unbranched polysaccharide chains (glycosaminoglycans) attached to protein cores. Common proteoglycans include aggrecan, betaglycan, decorin, perlecan, serglycin, and syndecan-1. Some of these molecules not only provide mechanical support, but also bind to extracellular signaling molecules,

15   such as fibroblast growth factor and transforming growth factor β, suggesting a role for proteoglycans in cell-cell communication. (Reviewed in Alberts, supra, pp. 973-978.)

Dentin phosphoryn (DPP) is a major component of the dentin ECM. DPP is a proteoglycan that is synthesized and expressed by odontoblasts (Gu, K., et al. (1998) Eur. J. Oral Sci. 106:1043-1047). DPP is believed to nucleate or modulate the formation of hydroxyapatite crystals.

20   Mucins are highly glycosylated glycoproteins that are the major structural component of the mucus gel. The physiological functions of mucins are cytoprotection, mechanical protection, maintenance of viscosity in secretions, and cellular recognition. MUC6 is a human gastric mucin that is also found in gall bladder, pancreas, seminal vesicles, and female reproductive tract (Toribara, N.W., et al. (1997) J. Biol. Chem. 272:16398-16403). The MUC6 gene has been mapped to human

25   chromosome 11 (Toribara, N.W., et al. (1993) J. Biol. Chem. 268:5879-5885). Hemomucin is a novel Drosophila surface mucin that may be involved in the induction of antibacterial effector molecules (Theopold, U., et al. (1996) J. Biol. Chem. 217:12708-12715).

Extracellular matrix proteins may regulate cellular protein activity in a variety of ways. Reversible protein phosphorylation is the primary method for regulating protein activity in eukaryotic

30   cells. In general, proteins are activated by phosphorylation in response to extracellular signals such as hormones, neurotransmitters, and growth and differentiation factors. The activated proteins initiate the cell's intracellular response by way of intracellular signaling pathways and second messenger molecules such as cyclic nucleotides, calcium-calmodulin, inositol, and various mitogens, that regulate protein phosphorylation.

Adhesi n-Associated Proteins

The surface of a cell is rich in transmembrane proteoglycans, glycoproteins, glycolipids, and receptors. These macromolecules mediate adhesion with other cells and with components of the ECM. The interaction of the cell with its surroundings profoundly influences cell shape, strength, flexibility,

5   motility, and adhesion. These dynamic properties are intimately associated with signal transduction pathways controlling cell proliferation and differentiation, tissue construction, and embryonic development.

Cadherins comprise a family of calcium-dependent glycoproteins that function in mediating cell-cell adhesion in virtually all solid tissues of multicellular organisms. These proteins share multiple

10 repeats of a cadherin-specific motif, and the repeats form the folding units of the cadherin ECM. Cadherin molecules cooperate to form focal contacts, or adhesion plaques, between adjacent epithelial cells. The cadherin family includes the classical cadherins and protocadherins. Classical cadherins include the E-cadherin, N-cadherin, and P-cadherin subfamilies. E-cadherin is present on many types of epithelial cells and is especially important for embryonic development. P-cadherin is present on cells

15 of the placenta and epidermis. Recent studies report that protocadherins are involved in a variety of cell-cell interactions (Suzuki, S. T. (1996) J. Cell Sci. 109:2609-2611). The intracellular anchorage of cadherins is regulated by their dynamic association with catenins, a family of cytoplasmic signal transduction proteins associated with the actin cytoskeleton. The anchorage of cadherins to the actin cytoskeleton appears to be regulated by protein tyrosine phosphorylation, and the cadherins are the

20 target of phosphorylation-induced junctional disassembly (Aberle, H., et al. (1996) J. Cell. Biochem. 61:514-523).

Integrins are ubiquitous transmembrane adhesion molecules that link the ECM to the internal cytoskeleton. Integrins are composed of two noncovalently associated transmembrane glycoprotein subunits called α and β. Integrins function as receptors that play a role in signal transduction. For

25 example, binding of integrin to its extracellular ligand may stimulate changes in intracellular calcium levels or protein kinase activity (Sjaastad, M.D. and Nelson, W.J. (1997) BioEssays 19:47-55).

Lectins comprise a ubiquitous family of extracellular glycoproteins which bind cell surface carbohydrates specifically and reversibly, resulting in the agglutination of cells. (Reviewed in Drickamer, K. and Taylor, M.E. (1993) Annu. Rev. Cell Biol. 9:237-264.) This function is

30 particularly important for activation of the immune response. Lectins mediate the agglutination and mitogenic stimulation of lymphocytes at sites of inflammation (Lasky, L.A. (1991) J. Cell. Biochem. 45:139-146; Paietta, E., et al. (1989) J. Immunol. 143:2850-2857). C-type lectin domains are found in a variety of proteins, including selectins and lecticans. Lecticans are a family of chondroitin sulfate proteoglycans that include aggrecan, versican, neurocan, and brevican. All C-type lectin proteins are

involved in protein-protein interactions (Aspberg, A., et al. (1997) Proc. Natl. Acad. Sci. USA 94:10116-10121). A novel macrophage-restricted C-type lectin protein has been cloned from mouse tissue. It is a type II transmembrane protein with one extracellular C-type lectin domain (Balch, S.G., et al. (1998) J. Biol. Chem. 273:18656-18664).

5   Toposome is a cell-adhesion glycoprotein isolated from mesenchyme-blastula embryos. Toposome precursors including vitellogenin promote cell adhesion of dissociated blastula cells.

           LRRs are sequence motifs, approximately 22-28 amino acids in length, found in proteins with a large variety of functions and cellular locations. Proteins containing LRRs are all thought to be involved in protein-protein interactions. The crystal structure of LRRs has been studied and found to

10   correspond to beta-alpha structural units. These structural units form a parallel beta sheet with one surface exposed to solvent. In this way an LRR-containing protein acquires a nonglobular shape (Kobe, B. and Deisenhofer, J. (1994) Trends Biochem. Sci. 19:415-421). There is evidence to suggest LRRs function in signal transduction and cellular adhesion as well as in protein-protein interactions (Gay, N.J., et al. (1991) FEBS Lett. 29:87-91).

15   Various proteins such as those encoded by the _Drosophila_ armadillo gene and the human APC gene contain amino acid repeats that interact with β-catenins. The armadillo gene is required for pattern formation within the embryonic segments and imaginal discs and is highly conserved. It is 63% identical to a human protein, plakoglobin, which is involved in adhesive junctions joining epithelial and other cells (Peifer, M. and Wieschaus, E. (1990) Cell 63:1167-1176). APC gene mutations appear to

20   initiate inherited forms of human colorectal cancer and sporadic forms of colorectal and gastric cancer (Rubinfeld, B., et al. (1993) Science 262:1731-1734). The fact that the protein encoded by APC interacts with catenin suggests a link between tumor initiation and cell adhesion (Su, L.K., et al. (1993) Science 262:1734-1737).

           SH3 is a 60-70 amino acid motif found in a variety of signal transduction and cytoskeletal

25   proteins. The SH3 domain is involved in mediating protein-protein interactions. Evidence suggests that the SH3 domains recognize a family of related domains or proteins in a variety of different tissues and species. One novel SH3 domain-containing protein is the 52 kilodalton focal adhesion protein (FAP52 or p52). FAP52 is localized to focal adhesions, specialized membrane domains in cultured cells that mediate the attachment of cells to the growth substratum and ECM. Focal adhesions consist of

30   structural proteins, integrins, regulatory molecules, and signaling molecules and are involved in cell signaling. FAP52 may form part of this multimolecular complex that comprises focal adhesion sites (Merilainent, J., et al. (1997) J. Biol. Chem. 272:23278-23284).

           The discovery of new extracellular matrix and cell adhesion molecules and the polynucleotides encoding them satisfies a need in the art by providing new compositions which are useful in the

4

diagnosis, prevention, and treatment of genetic, autoimmune/inflammation, and cell proliferative

disorders, including cancer, and in the assessment of the effects of exogenous compounds on the

expression of nucleic acid and amino acid sequences of extracellular matrix and cell adhesion

molecules.

5

SUMMARY OF THE INVENTION

The invention features purified polypeptides, extracellular matrix and cell adhesion molecules,

referred to collectively as "XMAD" and individually as "XMAD-1," "XMAD-2," "XMAD-3,"

"XMAD-4," "XMAD-5," "XMAD-6," "XMAD-7," "XMAD-8," "XMAD-9," "XMAD-10,"

10   "XMAD-11," "XMAD-12," "XMAD-13," "XMAD-14," "XMAD-15," "XMAD-16," "XMAD-17,"

"XMAD-18,""XMAD-19," "XMAD-20," and "XMAD-21." In one aspect, the invention provides an

isolated polypeptide comprising an amino acid sequence selected from the group consisting of a) an

amino acid sequence selected from the group consisting of SEQ ID NO:1-21, b) a naturally occurring

amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the

15   group consisting of SEQ ID NO:1-21, c) a biologically active fragment of an amino acid sequence

selected from the group consisting of SEQ ID NO:1-21, and d) an immunogenic fragment of an amino

acid sequence selected from the group consisting of SEQ ID NO:1-21. In one alternative, the invention

provides an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1-21.

The invention further provides an isolated polynucleotide encoding a polypeptide comprising an

20   amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the

group consisting of SEQ ID NO:1-21, b) a naturally occurring amino acid sequence having at least

90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-

21, c) a biologically active fragment of an amino acid sequence selected from the group consisting of

SEQ ID NO:1-21, and d) an immunogenic fragment of an amino acid sequence selected from the group

25   consisting of SEQ ID NO:1-21. In one alternative, the polynucleotide encodes a polypeptide selected

from the group consisting of SEQ ID NO:1-21. In another alternative, the polynucleotide is selected

from the group consisting of SEQ ID NO:22-42.

Additionally, the invention provides a recombinant polynucleotide comprising a promoter

sequence operably linked to a polynucleotide encoding a polypeptide comprising an amino acid

30   sequence selected from the group consisting of a) an amino acid sequence selected from the group

consisting of SEQ ID NO:1-21, b) a naturally occurring amino acid sequence having at least 90%

sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-21, c)

a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID

NO:1-21, and d) an immunogenic fragment of an amino acid sequence selected from the group

consisting of SEQ ID NO:1-21. In one alternative, the invention provides a cell transformed with the recombinant polynucleotide. In another alternative, the invention provides a transgenic organism comprising the recombinant polynucleotide.

The invention also provides a method for producing a polypeptide comprising an amino acid

5   sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-21, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-21, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-21, and d) an immunogenic fragment of an amino acid sequence selected from the group

10   consisting of SEQ ID NO:1-21. The method comprises a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding the polypeptide, and b) recovering the polypeptide so expressed.

Additionally, the invention provides an isolated antibody which specifically binds to a

15   polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-21, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-21, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-21, and d) an immunogenic fragment of an amino acid

20   sequence selected from the group consisting of SEQ ID NO:1-21.

The invention further provides an isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:22-42, b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:22-42, c) a

25   polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) an RNA equivalent of a)-d). In one alternative, the polynucleotide comprises at least 60 contiguous nucleotides.

Additionally, the invention provides a method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide comprising a polynucleotide sequence

30   selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:22-42, b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:22-42, c) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) an RNA equivalent of a)-d). The method comprises a) hybridizing the sample with a probe comprising

at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide

in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions

whereby a hybridization complex is formed between said probe and said target polynucleotide or

fragments thereof, and b) detecting the presence or absence of said hybridization complex, and

5   optionally, if present, the amount thereof. In one alternative, the probe comprises at least 60 contiguous

nucleotides.

The invention further provides a method for detecting a target polynucleotide in a sample, said

target polynucleotide having a sequence of a polynucleotide comprising a polynucleotide sequence

selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of

10   SEQ ID NO:22-42, b) a naturally occurring polynucleotide sequence having at least 90% sequence

identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:22-42, c) a

polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e)

an RNA equivalent of a)-d). The method comprises a) amplifying said target polynucleotide or

fragment thereof using polymerase chain reaction amplification, and b) detecting the presence or

15   absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the

amount thereof.

The invention further provides a composition comprising an effective amount of a polypeptide

comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence

selected from the group consisting of SEQ ID NO:1-21, b) a naturally occurring amino acid sequence

20   having at least 90% sequence identity to an amino acid sequence selected from the group consisting of

SEQ ID NO:1-21, c) a biologically active fragment of an amino acid sequence selected from the group

consisting of SEQ ID NO:1-21, and d) an immunogenic fragment of an amino acid sequence selected

from the group consisting of SEQ ID NO:1-21, and a pharmaceutically acceptable excipient. In one

embodiment, the composition comprises an amino acid sequence selected from the group consisting of

25   SEQ ID NO:1-21. The invention additionally provides a method of treating a disease or condition

associated with decreased expression of functional XMAD, comprising administering to a patient in

need of such treatment the composition.

The invention also provides a method for screening a compound for effectiveness as an

agonist of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an

30   amino acid sequence selected from the group consisting of SEQ ID NO:1-21, b) a naturally occurring

amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the

group consisting of SEQ ID NO:1-21, c) a biologically active fragment of an amino acid sequence

selected from the group consisting of SEQ ID NO:1-21, and d) an immunogenic fragment of an amino

acid sequence selected from the group consisting of SEQ ID NO:1-21. The method comprises a)

exposing a sample comprising the polypeptide to a compound, and b) detecting agonist activity in the sample. In one alternative, the invention provides a composition comprising an agonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with decreased expression of

5   functional XMAD, comprising administering to a patient in need of such treatment the composition.

Additionally, the invention provides a method for screening a compound for effectiveness as an antagonist of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-21, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence

10   selected from the group consisting of SEQ ID NO:1-21, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-21, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-21. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting antagonist activity in the sample. In one alternative, the invention provides a composition comprising

15   an antagonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with overexpression of functional XMAD, comprising administering to a patient in need of such treatment the composition.

The invention further provides a method of screening for a compound that specifically binds

20   to a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-21, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-21, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-21, and d) an immunogenic fragment of an amino acid

25   sequence selected from the group consisting of SEQ ID NO:1-21. The method comprises a) combining the polypeptide with at least one test compound under suitable conditions, and b) detecting binding of the polypeptide to the test compound, thereby identifying a compound that specifically binds to the polypeptide.

The invention further provides a method of screening for a compound that modulates the

30   activity of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-21, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-21, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-21, and d) an immunogenic

35   fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-21. The

method comprises a) combining the polypeptide with at least one test compound under conditions permissive for the activity of the polypeptide, b) assessing the activity of the polypeptide in the presence of the test compound, and c) comparing the activity of the polypeptide in the presence of the test compound with the activity of the polypeptide in the absence of the test compound, wherein a

5   change in the activity of the polypeptide in the presence of the test compound is indicative of a compound that modulates the activity of the polypeptide.

The invention further provides a method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence selected from the group consisting of SEQ ID NO:22-42, the method comprising a)

10 exposing a sample comprising the target polynucleotide to a compound, and b) detecting altered expression of the target polynucleotide.

The invention further provides a method for assessing toxicity of a test compound, said method comprising a) treating a biological sample containing nucleic acids with the test compound; b) hybridizing the nucleic acids of the treated biological sample with a probe comprising at least 20

15 contiguous nucleotides of a polynucleotide comprising a polynucleotide sequence selected from the group consisting of i) a polynucleotide sequence selected from the group consisting of SEQ ID NO:22-42, ii) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:22-42, iii) a polynucleotide sequence complementary to i), iv) a polynucleotide sequence complementary to ii),

20 and v) an RNA equivalent of i)-iv). Hybridization occurs under conditions whereby a specific hybridization complex is formed between said probe and a target polynucleotide in the biological sample, said target polynucleotide comprising a polynucleotide sequence selected from the group consisting of i) a polynucleotide sequence selected from the group consisting of SEQ ID NO:22-42, ii) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a

25 polynucleotide sequence selected from the group consisting of SEQ ID NO:22-42, iii) a polynucleotide sequence complementary to i), iv) a polynucleotide sequence complementary to ii), and v) an RNA equivalent of i)-iv). Alternatively, the target polynucleotide comprises a fragment of a polynucleotide sequence selected from the group consisting of i)-v) above; c) quantifying the amount of hybridization complex; and d) comparing the amount of hybridization complex in the

30 treated biological sample with the amount of hybridization complex in an untreated biological sample, wherein a difference in the amount of hybridization complex in the treated biological sample is indicative of toxicity of the test compound.

BRIEF DESCRIPTION OF THE TABLES

35   Table 1 shows polypeptide and nucleotide sequence identification numbers (SEQ ID NOs),

clone identification numbers (clone IDs), cDNA libraries, and cDNA fragments used to assemble full-length sequences encoding XMAD.

Table 2 shows features of each polypeptide sequence, including potential motifs, homologous sequences, and methods, algorithms, and searchable databases used for analysis of XMAD.

5   Table 3 shows selected fragments of each nucleic acid sequence; the tissue-specific expression patterns of each nucleic acid sequence as determined by northern analysis; diseases, disorders, or conditions associated with these tissues; and the vector into which each cDNA was cloned.

Table 4 describes the tissues used to construct the cDNA libraries from which cDNA clones encoding XMAD were isolated.

10   Table 5 shows the tools, programs, and algorithms used to analyze the polynucleotides and polypeptides of the invention, along with applicable descriptions, references, and threshold parameters.

DESCRIPTION OF THE INVENTION

Before the present proteins, nucleotide sequences, and methods are described, it is understood

15   that this invention is not limited to the particular machines, materials and methods described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a," "an,"

20   and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a host cell" includes a plurality of such host cells, and a reference to "an antibody" is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings

25   as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any machines, materials, and methods similar or equivalent to those described herein can be used to practice or test the present invention, the preferred machines, materials and methods are now described. All publications mentioned herein are cited for the purpose of describing and disclosing the cell lines, protocols, reagents and vectors which are reported in the publications and which might be used in

30   connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

DEFINITIONS

"XMAD" refers to the amino acid sequences of substantially purified XMAD obtained from any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and

10

human, and from any source, whether natural, synthetic, semi-synthetic, or recombinant.

The term "agonist" refers to a molecule which intensifies or mimics the biological activity of XMAD. Agonists may include proteins, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of XMAD either by directly interacting with

5   XMAD or by acting on components of the biological pathway in which XMAD participates.

An "allelic variant" is an alternative form of the gene encoding XMAD. Allelic variants may result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered. A gene may have none, one, or many allelic variants of its naturally occurring form. Common mutational changes which give rise to

10 allelic variants are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone, or in combination with the others, one or more times in a given sequence.

"Altered" nucleic acid sequences encoding XMAD include those sequences with deletions, insertions, or substitutions of different nucleotides, resulting in a polypeptide the same as XMAD or a

15 polypeptide with at least one functional characteristic of XMAD. Included within this definition are polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe of the polynucleotide encoding XMAD, and improper or unexpected hybridization to allelic variants, with a locus other than the normal chromosomal locus for the polynucleotide sequence encoding XMAD. The encoded protein may also be "altered," and may contain deletions, insertions, or substitutions of

20 amino acid residues which produce a silent change and result in a functionally equivalent XMAD. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological or immunological activity of XMAD is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, and positively charged amino acids may include

25 lysine and arginine. Amino acids with uncharged polar side chains having similar hydrophilicity values may include: asparagine and glutamine; and serine and threonine. Amino acids with uncharged side chains having similar hydrophilicity values may include: leucine, isoleucine, and valine; glycine and alanine; and phenylalanine and tyrosine.

The terms "amino acid" and "amino acid sequence" refer to an oligopeptide, peptide,

30 polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic molecules. Where "amino acid sequence" is recited to refer to a sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms are not meant to limit the amino acid sequence to the complete native amino acid sequence associated with the recited protein molecule.

"Amplification" relates to the production of additional copies of a nucleic acid sequence.

35 Amplification is generally carried out using polymerase chain reaction (PCR) technologies well known

in the art.

The term "antagonist" refers to a molecule which inhibits or attenuates the biological activity of XMAD. Antagonists may include proteins such as antibodies, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of XMAD either by

5   directly interacting with XMAD or by acting on components of the biological pathway in which XMAD participates.

The term "antibody" refers to intact immunoglobulin molecules as well as to fragments thereof, such as Fab, F(ab')$_2$, and Fv fragments, which are capable of binding an epitopic determinant. Antibodies that bind XMAD polypeptides can be prepared using intact polypeptides or using fragments

10   containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize the animal.

15   The term "antigenic determinant" refers to that region of a molecule (i.e., an epitope) that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (particular regions or three-dimensional structures on the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen used to

20   elicit the immune response) for binding to an antibody.

The term "antisense" refers to any composition capable of base-pairing with the "sense" (coding) strand of a specific nucleic acid sequence. Antisense compositions may include DNA; RNA; peptide nucleic acid (PNA); oligonucleotides having modified backbone linkages such as phosphorothioates, methylphosphonates, or benzylphosphonates; oligonucleotides having modified

25   sugar groups such as 2'-methoxyethyl sugars or 2'-methoxyethoxy sugars; or oligonucleotides having modified bases such as 5-methyl cytosine, 2'-deoxyuracil, or 7-deaza-2'-deoxyguanosine. Antisense molecules may be produced by any method including chemical synthesis or transcription. Once introduced into a cell, the complementary antisense molecule base-pairs with a naturally occurring nucleic acid sequence produced by the cell to form duplexes which block either transcription or

30   translation. The designation "negative" or "minus" can refer to the antisense strand, and the designation "positive" or "plus" can refer to the sense strand of a reference DNA molecule.

The term "biologically active" refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. Likewise, "immunologically active" or "immunogenic" refers to the capability of the natural, recombinant, or synthetic XMAD, or of any oligopeptide thereof,

to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

"Complementary" describes the relationship between two single-stranded nucleic acid sequences that anneal by base-pairing. For example, 5'-AGT-3' pairs with its complement, 3'-TCA-5'.

A "composition comprising a given polynucleotide sequence" and a "composition comprising a given amino acid sequence" refer broadly to any composition containing the given polynucleotide or amino acid sequence. The composition may comprise a dry formulation or an aqueous solution. Compositions comprising polynucleotide sequences encoding XMAD or fragments of XMAD may be employed as hybridization probes. The probes may be stored in freeze-dried form and may be associated with a stabilizing agent such as a carbohydrate. In hybridizations, the probe may be deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl sulfate; SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

"Consensus sequence" refers to a nucleic acid sequence which has been subjected to repeated DNA sequence analysis to resolve uncalled bases, extended using the XL-PCR kit (Applied Biosystems, Foster City CA) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from one or more overlapping cDNA, EST, or genomic DNA fragments using a computer program for fragment assembly, such as the GELVIEW fragment assembly system (GCG, Madison WI) or Phrap (University of Washington, Seattle WA). Some sequences have been both extended and assembled to produce the consensus sequence.

"Conservative amino acid substitutions" are those substitutions that are predicted to least interfere with the properties of the original protein, i.e., the structure and especially the function of the protein is conserved and not significantly changed by such substitutions. The table below shows amino acids which may be substituted for an original amino acid in a protein and which are regarded as conservative amino acid substitutions.

Original Residue	Conservative Substitution
Ala	Gly, Ser
Arg	His, Lys
Asn	Asp, Gln, His
Asp	Asn, Glu
Cys	Ala, Ser
Gln	Asn, Glu, His
Glu	Asp, Gln, His
Gly	Ala
His	Asn, Arg, Gln, Glu
Ile	Leu, Val
Leu	Ile, Val
Lys	Arg, Gln, Glu

13

Met	Leu, Ile
Phe	His, Met, Leu, Trp, Tyr
Ser	Cys, Thr
Thr	Ser, Val
Trp	Phe, Tyr
Tyr	His, Phe, Trp
Val	Ile, Leu, Thr

Conservative amino acid substitutions generally maintain (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a beta sheet or alpha helical conformation, (b) the charge or hydrophobicity of the molecule at the site of the substitution, and/or (c) the bulk of the side chain.

A "deletion" refers to a change in the amino acid or nucleotide sequence that results in the absence of one or more amino acid residues or nucleotides.

The term "derivative" refers to a chemically modified polynucleotide or polypeptide. Chemical modifications of a polynucleotide sequence can include, for example, replacement of hydrogen by an alkyl, acyl, hydroxyl, or amino group. A derivative polynucleotide encodes a polypeptide which retains at least one biological or immunological function of the natural molecule. A derivative polypeptide is one modified by glycosylation, pegylation, or any similar process that retains at least one biological or immunological function of the polypeptide from which it was derived.

A "detectable label" refers to a reporter molecule or enzyme that is capable of generating a measurable signal and is covalently or noncovalently joined to a polynucleotide or polypeptide.

A "fragment" is a unique portion of XMAD or the polynucleotide encoding XMAD which is identical in sequence to but shorter in length than the parent sequence. A fragment may comprise up to the entire length of the defined sequence, minus one nucleotide/amino acid residue. For example, a fragment may comprise from 5 to 1000 contiguous nucleotides or amino acid residues. A fragment used as a probe, primer, antigen, therapeutic molecule, or for other purposes, may be at least 5, 10, 15, 16, 20, 25, 30, 40, 50, 60, 75, 100, 150, 250 or at least 500 contiguous nucleotides or amino acid residues in length. Fragments may be preferentially selected from certain regions of a molecule. For example, a polypeptide fragment may comprise a certain length of contiguous amino acids selected from the first 250 or 500 amino acids (or first 25% or 50% of a polypeptide) as shown in a certain defined sequence. Clearly these lengths are exemplary, and any length that is supported by the specification, including the Sequence Listing, tables, and figures, may be encompassed by the present embodiments.

A fragment of SEQ ID NO:22-42 comprises a region of unique polynucleotide sequence that specifically identifies SEQ ID NO:22-42, for example, as distinct from any other sequence in the genome from which the fragment was obtained. A fragment of SEQ ID NO:22-42 is useful, for

example, in hybridization and amplification technologies and in analogous methods that distinguish SEQ ID NO:22-42 from related polynucleotide sequences. The precise length of a fragment of SEQ ID NO:22-42 and the region of SEQ ID NO:22-42 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

5   A fragment of SEQ ID NO:1-21 is encoded by a fragment of SEQ ID NO:22-42. A fragment of SEQ ID NO:1-21 comprises a region of unique amino acid sequence that specifically identifies SEQ ID NO:1-21. For example, a fragment of SEQ ID NO:1-21 is useful as an immunogenic peptide for the development of antibodies that specifically recognize SEQ ID NO:1-21. The precise length of a fragment of SEQ ID NO:1-21 and the region of SEQ ID NO:1-21 to which the fragment

10   corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

        A "full-length" polynucleotide sequence is one containing at least a translation initiation codon (e.g., methionine) followed by an open reading frame and a translation termination codon. A "full-length" polynucleotide sequence encodes a "full-length" polypeptide sequence.

15   "Homology" refers to sequence similarity or, interchangeably, sequence identity, between two or more polynucleotide sequences or two or more polypeptide sequences.

        The terms "percent identity" and "% identity," as applied to polynucleotide sequences, refer to the percentage of residue matches between at least two polynucleotide sequences aligned using a standardized algorithm. Such an algorithm may insert, in a standardized and reproducible way, gaps in

20   the sequences being compared in order to optimize alignment between two sequences, and therefore achieve a more meaningful comparison of the two sequences.

        Percent identity between polynucleotide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program. This program is part of the LASERGENE software package, a suite of molecular

25   biological analysis programs (DNASTAR, Madison WI). CLUSTAL V is described in Higgins, D.G. and P.M. Sharp (1989) CABIOS 5:151-153 and in Higgins, D.G. et al. (1992) CABIOS 8:189-191. For pairwise alignments of polynucleotide sequences, the default parameters are set as follows: Ktuple=2, gap penalty=5, window=4, and "diagonals saved"=4. The "weighted" residue weight table is selected as the default. Percent identity is reported by CLUSTAL V as the "percent similarity" between

30   aligned polynucleotide sequences.

        Alternatively, a suite of commonly used and freely available sequence comparison algorithms is provided by the National Center for Biotechnology Information (NCBI) Basic Local Alignment Search Tool (BLAST) (Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410), which is available from several sources, including the NCBI, Bethesda, MD, and on the Internet at

35   http://www.ncbi.nlm.nih.gov/BLAST/. The BLAST software suite includes various sequence analysis

15

programs including "blastn," that is used to align a known polynucleotide sequence with other polynucleotide sequences from a variety of databases. Also available is a tool called "BLAST 2 Sequences" that is used for direct pairwise comparison of two nucleotide sequences. "BLAST 2 Sequences" can be accessed and used interactively at http://www.ncbi.nlm.nih.gov/gorf/bl2.html. The

5   "BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below). BLAST programs are commonly used with gap and other parameters set to default settings. For example, to compare two nucleotide sequences, one may use blastn with the "BLAST 2 Sequences" tool Version 2.0.12 (April-21-2000) set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62

10   *Reward for match: 1*

Penalty for mismatch: -2

Open Gap: 5 and Extension Gap: 2 penalties

Gap x drop-off: 50

Expect: 10

15   *Word Size: 11*

Filter: on

Percent identity may be measured over the length of an entire defined sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined sequence, for instance, a fragment of at least 20, at

20   least 30, at least 40, at least 50, at least 70, at least 100, or at least 200 contiguous nucleotides. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures, or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

Nucleic acid sequences that do not show a high degree of identity may nevertheless encode

25   similar amino acid sequences due to the degeneracy of the genetic code. It is understood that changes in a nucleic acid sequence can be made using this degeneracy to produce multiple nucleic acid sequences that all encode substantially the same protein.

The phrases "percent identity" and "% identity," as applied to polypeptide sequences, refer to the percentage of residue matches between at least two polypeptide sequences aligned using a

30   standardized algorithm. Methods of polypeptide sequence alignment are well-known. Some alignment methods take into account conservative amino acid substitutions. Such conservative substitutions, explained in more detail above, generally preserve the charge and hydrophobicity at the site of substitution, thus preserving the structure (and therefore function) of the polypeptide.

Percent identity between polypeptide sequences may be determined using the default parameters

of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program (described and referenced above). For pairwise alignments of polypeptide sequences using CLUSTAL V, the default parameters are set as follows: Ktuple=1, gap penalty=3, window=5, and "diagonals saved"=5. The PAM250 matrix is selected as the default residue weight table. As with

5   polynucleotide alignments, the percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polypeptide sequence pairs.

Alternatively the NCBI BLAST software suite may be used. For example, for a pairwise comparison of two polypeptide sequences, one may use the "BLAST 2 Sequences" tool Version 2.0.12 (Apr-21-2000) with blastp set at default parameters. Such default parameters may be, for example:

10   *Matrix: BLOSUM62*

Open Gap: 11 and Extension Gap: 1 penalties

Gap x drop-off: 50

Expect: 10

Word Size: 3

15   *Filter: on*

Percent identity may be measured over the length of an entire defined polypeptide sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined polypeptide sequence, for instance, a fragment of at least 15, at least 20, at least 30, at least 40, at least 50, at least 70 or at least 150

20   contiguous residues. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

"Human artificial chromosomes" (HACs) are linear microchromosomes which may contain DNA sequences of about 6 kb to 10 Mb in size, and which contain all of the elements required for

25   chromosome replication, segregation and maintenance.

The term "humanized antibody" refers to an antibody molecule in which the amino acid sequence in the non-antigen binding regions has been altered so that the antibody more closely resembles a human antibody, and still retains its original binding ability.

"Hybridization" refers to the process by which a polynucleotide strand anneals with a

30   complementary strand through base pairing under defined hybridization conditions. Specific hybridization is an indication that two nucleic acid sequences share a high degree of complementarity. Specific hybridization complexes form under permissive annealing conditions and remain hybridized after the "washing" step(s). The washing step(s) is particularly important in determining the stringency of the hybridization process, with more stringent conditions allowing less non-specific binding, i.e.,

binding between pairs of nucleic acid strands that are not perfectly matched. Permissive conditions for annealing of nucleic acid sequences are routinely determinable by one of ordinary skill in the art and may be consistent among hybridization experiments, whereas wash conditions may be varied among experiments to achieve the desired stringency, and therefore hybridization specificity. Permissive

5 annealing conditions occur, for example, at 68°C in the presence of about 6 x SSC, about 1% (w/v) SDS, and about 100 µg/ml sheared, denatured salmon sperm DNA.

Generally, stringency of hybridization is expressed, in part, with reference to the temperature under which the wash step is carried out. Such wash temperatures are typically selected to be about 5°C to 20°C lower than the thermal melting point (T_m) for the specific sequence at a defined ionic

10 strength and pH. The T_m is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. An equation for calculating T_m and conditions for nucleic acid hybridization are well known and can be found in Sambrook, J. et al., 1989, Molecular Cloning: A Laboratory Manual, 2nd ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; specifically see volume 2, chapter 9.

15 High stringency conditions for hybridization between polynucleotides of the present invention include wash conditions of 68°C in the presence of about 0.2 x SSC and about 0.1% SDS, for 1 hour. Alternatively, temperatures of about 65°C, 60°C, 55°C, or 42°C may be used. SSC concentration may be varied from about 0.1 to 2 x SSC, with SDS being present at about 0.1%. Typically, blocking reagents are used to block non-specific hybridization. Such blocking reagents include, for instance,

20 sheared and denatured salmon sperm DNA at about 100-200 µg/ml. Organic solvent, such as formamide at a concentration of about 35-50% v/v, may also be used under particular circumstances, such as for RNA:DNA hybridizations. Useful variations on these wash conditions will be readily apparent to those of ordinary skill in the art. Hybridization, particularly under high stringency conditions, may be suggestive of evolutionary similarity between the nucleotides. Such similarity is

25 strongly indicative of a similar role for the nucleotides and their encoded polypeptides.

The term "hybridization complex" refers to a complex formed between two nucleic acid sequences by virtue of the formation of hydrogen bonds between complementary bases. A hybridization complex may be formed in solution (e.g., C_0t or R_0t analysis) or formed between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g.,

30 paper, membranes, filters, chips, pins or glass slides, or any other appropriate substrate to which cells or their nucleic acids have been fixed).

The words "insertion" and "addition" refer to changes in an amino acid or nucleotide sequence resulting in the addition of one or more amino acid residues or nucleotides, respectively.

"Immune response" can refer to conditions associated with inflammation, trauma, immune

disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect cellular and systemic defense systems.

An "immunogenic fragment" is a polypeptide or oligopeptide fragment of XMAD which is capable of eliciting an immune response when introduced into a living organism, for example, a mammal. The term "immunogenic fragment" also includes any polypeptide or oligopeptide fragment of XMAD which is useful in any of the antibody production methods disclosed herein or known in the art.

The term "microarray" refers to an arrangement of a plurality of polynucleotides, polypeptides, or other chemical compounds on a substrate.

The terms "element" and "array element" refer to a polynucleotide, polypeptide, or other chemical compound having a unique and defined position on a microarray.

The term "modulate" refers to a change in the activity of XMAD. For example, modulation may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional, or immunological properties of XMAD.

The phrases "nucleic acid" and "nucleic acid sequence" refer to a nucleotide, oligonucleotide, polynucleotide, or any fragment thereof. These phrases also refer to DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material.

"Operably linked" refers to the situation in which a first nucleic acid sequence is placed in a functional relationship with a second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding sequence. Operably linked DNA sequences may be in close proximity or contiguous and, where necessary to join two protein coding regions, in the same reading frame.

"Peptide nucleic acid" (PNA) refers to an antisense molecule or anti-gene agent which comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition. PNAs preferentially bind complementary single stranded DNA or RNA and stop transcript elongation, and may be pegylated to extend their lifespan in the cell.

"Post-translational modification" of an XMAD may involve lipidation, glycosylation, phosphorylation, acetylation, racemization, proteolytic cleavage, and other modifications known in the art. These processes may occur synthetically or biochemically. Biochemical modifications will vary by cell type depending on the enzymatic milieu of XMAD.

"Probe" refers to nucleic acid sequences encoding XMAD, their complements, or fragments thereof, which are used to detect identical, allelic or related nucleic acid sequences. Probes are isolated oligonucleotides or polynucleotides attached to a detectable label or reporter molecule. Typical

labels include radioactive isotopes, ligands, chemiluminescent agents, and enzymes. "Primers" are short nucleic acids, usually DNA oligonucleotides, which may be annealed to a target polynucleotide by complementary base-pairing. The primer may then be extended along the target DNA strand by a DNA polymerase enzyme. Primer pairs can be used for amplification (and identification) of a nucleic acid

5   sequence, e.g., by the polymerase chain reaction (PCR).

Probes and primers as used in the present invention typically comprise at least 15 contiguous nucleotides of a known sequence. In order to enhance specificity, longer probes and primers may also be employed, such as probes and primers that comprise at least 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, or at least 150 consecutive nucleotides of the disclosed nucleic acid sequences. Probes and primers may

10   be considerably longer than these examples, and it is understood that any length supported by the specification, including the tables, figures, and Sequence Listing, may be used.

Methods for preparing and using probes and primers are described in the references, for example Sambrook, J. et al. (1989) Molecular Cloning: A Laboratory Manual, 2nd ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; Ausubel, F.M. et al. (1987) Current Protocols in Molecular

15   Biology, Greene Publ. Assoc. & Wiley-Intersciences, New York NY; Innis, M. et al. (1990) PCR Protocols, A Guide to Methods and Applications, Academic Press, San Diego CA. PCR primer pairs can be derived from a known sequence, for example, by using computer programs intended for that purpose such as Primer (Version 0.5, 1991, Whitehead Institute for Biomedical Research, Cambridge MA).

20   Oligonucleotides for use as primers are selected using software known in the art for such purpose. For example, OLIGO 4.06 software is useful for the selection of PCR primer pairs of up to 100 nucleotides each, and for the analysis of oligonucleotides and larger polynucleotides of up to 5,000 nucleotides from an input polynucleotide sequence of up to 32 kilobases. Similar primer selection programs have incorporated additional features for expanded capabilities. For example, the PrimOU

25   primer selection program (available to the public from the Genome Center at University of Texas South West Medical Center, Dallas TX) is capable of choosing specific primers from megabase sequences and is thus useful for designing primers on a genome-wide scope. The Primer3 primer selection program (available to the public from the Whitehead Institute/MIT Center for Genome Research, Cambridge MA) allows the user to input a "mispriming library," in which sequences to avoid as primer

30   binding sites are user-specified. Primer3 is useful, in particular, for the selection of oligonucleotides for microarrays. (The source code for the latter two primer selection programs may also be obtained from their respective sources and modified to meet the user's specific needs.) The PrimeGen program (available to the public from the UK Human Genome Mapping Project Resource Centre, Cambridge UK) designs primers based on multiple sequence alignments, thereby allowing selection of primers that

hybridize to either the most conserved or least conserved regions of aligned nucleic acid sequences. Hence, this program is useful for identification of both unique and conserved oligonucleotides and polynucleotide fragments. The oligonucleotides and polynucleotide fragments identified by any of the above selection methods are useful in hybridization technologies, for example, as PCR or sequencing

5   primers, microarray elements, or specific probes to identify fully or partially complementary polynucleotides in a sample of nucleic acids. Methods of oligonucleotide selection are not limited to those described above.

A "recombinant nucleic acid" is a sequence that is not naturally occurring or has a sequence that is made by an artificial combination of two or more otherwise separated segments of sequence.

10   This artificial combination is often accomplished by chemical synthesis or, more commonly, by the artificial manipulation of isolated segments of nucleic acids, e.g., by genetic engineering techniques such as those described in Sambrook, supra. The term recombinant includes nucleic acids that have been altered solely by addition, substitution, or deletion of a portion of the nucleic acid. Frequently, a recombinant nucleic acid may include a nucleic acid sequence operably linked to a promoter sequence.

15   Such a recombinant nucleic acid may be part of a vector that is used, for example, to transform a cell.

Alternatively, such recombinant nucleic acids may be part of a viral vector, e.g., based on a vaccinia virus, that could be use to vaccinate a mammal wherein the recombinant nucleic acid is expressed, inducing a protective immunological response in the mammal.

A "regulatory element" refers to a nucleic acid sequence usually derived from untranslated

20   regions of a gene and includes enhancers, promoters, introns, and 5' and 3' untranslated regions (UTRs). Regulatory elements interact with host or viral proteins which control transcription, translation, or RNA stability.

"Reporter molecules" are chemical or biochemical moieties used for labeling a nucleic acid, amino acid, or antibody. Reporter molecules include radionuclides; enzymes; fluorescent,

25   chemiluminescent, or chromogenic agents; substrates; cofactors; inhibitors; magnetic particles; and other moieties known in the art.

An "RNA equivalent," in reference to a DNA sequence, is composed of the same linear sequence of nucleotides as the reference DNA sequence with the exception that all occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose

30   instead of deoxyribose.

The term "sample" is used in its broadest sense. A sample suspected of containing nucleic acids encoding XMAD, or fragments thereof, or XMAD itself, may comprise a bodily fluid; an extract from a cell, chromosome, organelle, or membrane isolated from a cell; a cell; genomic DNA, RNA, or cDNA, in solution or bound to a substrate; a tissue; a tissue print; etc.

The terms "specific binding" and "specifically binding" refer to that interaction between a protein or peptide and an agonist, an antibody, an antagonist, a small molecule, or any natural or synthetic binding composition. The interaction is dependent upon the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For

5   example, if an antibody is specific for epitope "A," the presence of a polypeptide comprising the epitope A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

The term "substantially purified" refers to nucleic acid or amino acid sequences that are removed from their natural environment and are isolated or separated, and are at least 60% free,

10   preferably at least 75% free, and most preferably at least 90% free from other components with which they are naturally associated.

A "substitution" refers to the replacement of one or more amino acid residues or nucleotides by different amino acid residues or nucleotides, respectively.

"Substrate" refers to any suitable rigid or semi-rigid support including membranes, filters,

15   chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers, microparticles and capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polynucleotides or polypeptides are bound.

A "transcript image" refers to the collective pattern of gene expression by a particular cell type or tissue under given conditions at a given time.

20   "Transformation" describes a process by which exogenous DNA is introduced into a recipient cell. Transformation may occur under natural or artificial conditions according to various methods well known in the art, and may rely on any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected based on the type of host cell being transformed and may include, but is not limited to, bacteriophage or viral infection,

25   electroporation, heat shock, lipofection, and particle bombardment. The term "transformed" cells includes stably transformed cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome, as well as transiently transformed cells which express the inserted DNA or RNA for limited periods of time.

A "transgenic organism," as used herein, is any organism, including but not limited to

30   animals and plants, in which one or more of the cells of the organism contains heterologous nucleic acid introduced by way of human intervention, such as by transgenic techniques well known in the art. The nucleic acid is introduced into the cell, directly or indirectly by introduction into a precursor of the cell, by way of deliberate genetic manipulation, such as by microinjection or by infection with a recombinant virus. The term genetic manipulation does not include classical cross-breeding, or in

35   vitro fertilization, but rather is directed to the introduction of a recombinant DNA molecule. The

transgenic organisms contemplated in accordance with the present invention include bacteria, cyanobacteria, fungi, plants, and animals. The isolated DNA of the present invention can be introduced into the host by methods known in the art, for example infection, transfection, transformation or transconjugation. Techniques for transferring the DNA of the present invention

5   into such organisms are widely known and provided in references such as Sambrook, J. et al. (1989), supra.

A "variant" of a particular nucleic acid sequence is defined as a nucleic acid sequence having at least 40% sequence identity to the particular nucleic acid sequence over a certain length of one of the nucleic acid sequences using blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999)

10 set at default parameters. Such a pair of nucleic acids may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95% or at least 98% or greater sequence identity over a certain defined length. A variant may be described as, for example, an "allelic" (as defined above), "splice," "species," or "polymorphic" variant. A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides

15 due to alternative splicing of exons during mRNA processing. The corresponding polypeptide may possess additional functional domains or lack domains that are present in the reference molecule. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides generally will have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given

20 species. Polymorphic variants also may encompass "single nucleotide polymorphisms" (SNPs) in which the polynucleotide sequence varies by one nucleotide base. The presence of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

A "variant" of a particular polypeptide sequence is defined as a polypeptide sequence having at least 40% sequence identity to the particular polypeptide sequence over a certain length of one of the

25 polypeptide sequences using blastp with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of polypeptides may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 98% or greater sequence identity over a certain defined length of one of the polypeptides.

THE INVENTION

30   The invention is based on the discovery of new human extracellular matrix and cell adhesion molecules (XMAD), the polynucleotides encoding XMAD, and the use of these compositions for the diagnosis, treatment, or prevention of genetic, autoimmune/inflammation, and cell proliferative disorders, including cancer.

Table 1 lists the Incyte clones used to assemble full length nucleotide sequences encoding

35 XMAD. Columns 1 and 2 show the sequence identification numbers (SEQ ID NOs) of the polypeptide

and nucleotide sequences, respectively. Column 3 shows the clone IDs of the Incyte clones in which

nucleic acids encoding each XMAD were identified, and column 4 shows the cDNA libraries from

which these clones were isolated. Column 5 shows Incyte clones and their corresponding cDNA

libraries. Clones for which cDNA libraries are not indicated were derived from pooled cDNA libraries.

5   In some cases, GenBank sequence identifiers are also shown in column 5. The Incyte clones and

GenBank cDNA sequences, where indicated, in column 5 were used to assemble the consensus

nucleotide sequence of each XMAD and are useful as fragments in hybridization technologies.

The columns of Table 2 show various properties of each of the polypeptides of the invention:

column 1 references the SEQ ID NO; column 2 shows the number of amino acid residues in each

10   polypeptide; column 3 shows potential phosphorylation sites; column 4 shows potential glycosylation

sites; column 5 shows the amino acid residues comprising signature sequences and motifs; column 6

shows homologous sequences as identified by BLAST analysis along with relevant citations, all of

which are expressly incorporated by reference herein in their entirety; and column 7 shows analytical

methods and in some cases, searchable databases to which the analytical methods were applied. The

15   methods of column 7 were used to characterize each polypeptide through sequence homology and

protein motifs.

The columns of Table 3 show the tissue-specificity and diseases, disorders, or conditions

associated with nucleotide sequences encoding XMAD. The first column of Table 3 lists the nucleotide

SEQ ID NOs. Column 2 lists fragments of the nucleotide sequences of column 1. These fragments are

20   useful, for example, in hybridization or amplification technologies to identify SEQ ID NO:22-42 and

to distinguish between SEQ ID NO:22-42 and related polynucleotide sequences. The polypeptides

encoded by these fragments are useful, for example, as immunogenic peptides. Column 3 lists tissue

categories which express XMAD as a fraction of total tissues expressing XMAD. Column 4 lists

diseases, disorders, or conditions associated with those tissues expressing XMAD as a fraction of total

25   tissues expressing XMAD. Column 5 lists the vectors used to subclone each cDNA library.

The columns of Table 4 show descriptions of the tissues used to construct the cDNA libraries

from which cDNA clones encoding XMAD were isolated. Column 1 references the nucleotide SEQ ID

NOs, column 2 shows the cDNA libraries from which these clones were isolated, and column 3 shows

the tissue origins and other descriptive information relevant to the cDNA libraries in column 2.

30   SEQ ID NO:18 maps to chromosome 22 within the interval from the P terminus to 19.5

centiMorgans.

The invention also encompasses XMAD variants. A preferred XMAD variant is one which has

at least about 80%, or alternatively at least about 90%, or even at least about 95% amino acid sequence

identity to the XMAD amino acid sequence, and which contains at least one functional or structural

characteristic of XMAD.

The invention also encompasses polynucleotides which encode XMAD. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:22-42, which encodes XMAD. The polynucleotide sequences of

5   SEQ ID NO:22-42, as presented in the Sequence Listing, embrace the equivalent RNA sequences, wherein occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose instead of deoxyribose.

The invention also encompasses a variant of a polynucleotide sequence encoding XMAD. In particular, such a variant polynucleotide sequence will have at least about 70%, or alternatively at least

10   about 85%, or even at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding XMAD. A particular aspect of the invention encompasses a variant of a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:22-42 which has at least about 70%, or alternatively at least about 85%, or even at least about 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:22-42.

15   Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of XMAD.

It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding XMAD, some bearing minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the

20   invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally occurring XMAD, and all such variations are to be considered as being specifically disclosed.

Although nucleotide sequences which encode XMAD and its variants are generally capable of

25   hybridizing to the nucleotide sequence of the naturally occurring XMAD under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding XMAD or its derivatives possessing a substantially different codon usage, e.g., inclusion of non-naturally occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which

30   particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding XMAD and its derivatives without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode XMAD and

XMAD derivatives, or fragments thereof, entirely by synthetic chemistry. After production, the synthetic sequence may be inserted into any of the many available expression vectors and cell systems using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce mutations into a sequence encoding XMAD or any fragment thereof.

5   Also encompassed by the invention are polynucleotide sequences that are capable of hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in SEQ ID NO:22-42 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and S.L. Berger (1987) Methods Enzymol. 152:399-407; Kimmel, A.R. (1987) Methods Enzymol. 152:507-511.) Hybridization conditions, including annealing and wash conditions, are described in
10   "Definitions."

Methods for DNA sequencing are well known in the art and may be used to practice any of the embodiments of the invention. The methods may employ such enzymes as the Klenow fragment of DNA polymerase I, SEQUENASE (US Biochemical, Cleveland OH), Taq polymerase (Applied Biosystems, Foster City CA), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway
15   NJ), or combinations of polymerases and proofreading exonucleases such as those found in the ELONGASE amplification system (Life Technologies, Gaithersburg MD). Preferably, sequence preparation is automated with machines such as the MICROLAB 2200 liquid transfer system (Hamilton, Reno NV), PTC200 thermal cycler (MJ Research, Watertown MA) and ABI CATALYST 800 thermal cycler (Applied Biosystems). Sequencing is then carried out using either the ABI 373 or ·
20   377 DNA sequencing system (Applied Biosystems), the MEGABACE 1000 DNA sequencing system (Molecular Dynamics, Sunnyvale CA), or other systems known in the art. The resulting sequences are analyzed using a variety of algorithms which are well known in the art. (See, e.g., Ausubel, F.M. (1997) Short Protocols in Molecular Biology, John Wiley & Sons, New York NY, unit 7.7; Meyers, R.A. (1995) Molecular Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853.)

25   The nucleic acid sequences encoding XMAD may be extended utilizing a partial nucleotide sequence and employing various PCR-based methods known in the art to detect upstream sequences, such as promoters and regulatory elements. For example, one method which may be employed, restriction-site PCR, uses universal and nested primers to amplify unknown sequence from genomic DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) PCR Methods Applic. 2:318-322.)
30   Another method, inverse PCR, uses primers that extend in divergent directions to amplify unknown sequence from a circularized template. The template is derived from restriction fragments comprising a known genomic locus and surrounding sequences. (See, e.g., Triglia, T. et al. (1988) Nucleic Acids Res. 16:8186.) A third method, capture PCR, involves PCR amplification of DNA fragments adjacent to known sequences in human and yeast artificial chromosome DNA. (See, e.g., Lagerstrom, M. et al.

(1991) PCR Methods Applic. 1:111-119.) In this method, multiple restriction enzyme digestions and ligations may be used to insert an engineered double-stranded sequence into a region of unknown sequence before performing PCR. Other methods which may be used to retrieve unknown sequences are known in the art. (See, e.g., Parker, J.D. et al. (1991) Nucleic Acids Res. 19:3055-3060).

5   Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries (Clontech, Palo Alto CA) to walk genomic DNA. This procedure avoids the need to screen libraries and is useful in finding intron/exon junctions. For all PCR-based methods, primers may be designed using commercially available software, such as OLIGO 4.06 Primer Analysis software (National Biosciences, Plymouth MN) or another appropriate program, to be about 22 to 30 nucleotides in length, to have a

10   GC content of about 50% or more, and to anneal to the template at temperatures of about 68°C to 72°C.

When screening for full-length cDNAs, it is preferable to use libraries that have been size-selected to include larger cDNAs. In addition, random-primed libraries, which often include sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T) library

15   does not yield a full-length cDNA. Genomic libraries may be useful for extension of sequence into 5' non-transcribed regulatory regions.

Capillary electrophoresis systems which are commercially available may be used to analyze the size or confirm the nucleotide sequence of sequencing or PCR products. In particular, capillary sequencing may employ flowable polymers for electrophoretic separation, four different nucleotide-

20   specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for detection of the emitted wavelengths. Output/light intensity may be converted to electrical signal using appropriate software (e.g., GENOTYPER and SEQUENCE NAVIGATOR, Applied Biosystems), and the entire process from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments

25   which may be present in limited amounts in a particular sample.

In another embodiment of the invention, polynucleotide sequences or fragments thereof which encode XMAD may be cloned in recombinant DNA molecules that direct expression of XMAD, or fragments or functional equivalents thereof, in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent

30   amino acid sequence may be produced and used to express XMAD.

The nucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter XMAD-encoding sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic

27

oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

The nucleotides of the present invention may be subjected to DNA shuffling techniques such

5   as MOLECULARBREEDING (Maxygen Inc., Santa Clara CA; described in U.S. Patent Number 5,837,458; Chang, C.-C. et al. (1999) Nat. Biotechnol. 17:793-797; Christians, F.C. et al. (1999) Nat. Biotechnol. 17:259-264; and Crameri, A. et al. (1996) Nat. Biotechnol. 14:315-319) to alter or improve the biological properties of XMAD, such as its biological or enzymatic activity or its ability to bind to other molecules or compounds. DNA shuffling is a process by which a library of gene

10   variants is produced using PCR-mediated recombination of gene fragments. The library is then subjected to selection or screening procedures that identify those gene variants with the desired properties. These preferred variants may then be pooled and further subjected to recursive rounds of DNA shuffling and selection/screening. Thus, genetic diversity is created through "artificial" breeding and rapid molecular evolution. For example, fragments of a single gene containing random

15   point mutations may be recombined, screened, and then reshuffled until the desired properties are optimized. Alternatively, fragments of a given gene may be recombined with fragments of homologous genes in the same gene family, either from the same or different species, thereby maximizing the genetic diversity of multiple naturally occurring genes in a directed and controllable manner.

20   In another embodiment, sequences encoding XMAD may be synthesized, in whole or in part, using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al. (1980) Nucleic Acids Symp. Ser. 7:215-223; Horn, T. et al. (1980) Nucleic Acids Symp. Ser. 7:225-232.) Alternatively, XMAD itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solution-phase or solid-phase techniques. (See, e.g.,

25   Creighton, T. (1984) Proteins, Structures and Molecular Properties, WH Freeman, New York NY, pp. 55-60; and Roberge, J.Y. et al. (1995) Science 269:202-204.) Automated synthesis may be achieved using the ABI 431A peptide synthesizer (Applied Biosystems). Additionally, the amino acid sequence of XMAD, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other proteins, or any part thereof, to produce a variant polypeptide or a polypeptide having a

30   sequence of a naturally occurring polypeptide.

The peptide may be substantially purified by preparative high performance liquid chromatography. (See, e.g., Chiez, R.M. and F.Z. Regnier (1990) Methods Enzymol. 182:392-421.) The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing. (See, e.g., Creighton, supra, pp. 28-53.)

35   In order to express a biologically active XMAD, the nucleotide sequences encoding XMAD or

derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' untranslated regions in the vector and in polynucleotide sequences

5   encoding XMAD. Such elements may vary in their strength and specificity. Specific initiation signals may also be used to achieve more efficient translation of sequences encoding XMAD. Such signals include the ATG initiation codon and adjacent sequences, e.g. the Kozak sequence. In cases where sequences encoding XMAD and its initiation codon and upstream regulatory sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be

10   needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals including an in-frame ATG initiation codon should be provided by the vector. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used. (See, e.g., Scharf, D. et al. (1994) Results Probl. Cell Differ.

15   20:125-162.)

Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding XMAD and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory

20   Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and 16-17; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and 16.)

A variety of expression vector/host systems may be utilized to contain and express sequences encoding XMAD. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with

25   yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus); plant cell systems transformed with viral expression vectors (e.g., cauliflower mosaic virus, CaMV, or tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems. (See, e.g., Sambrook, supra; Ausubel, supra; Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509; Bitter, G.A. et al. (1987) Methods Enzymol. 153:516-544;

30   Scorer, C.A. et al. (1994) Bio/Technology 12:181-184; Engelhard, E.K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945; Takamatsu, N. (1987) EMBO J. 6:307-311; Coruzzi, G. et al. (1984) EMBO J. 3:1671-1680; Broglie, R. et al. (1984) Science 224:838-843; Winter, J. et al. (1991) Results Probl. Cell Differ. 17:85-105; The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp.

35   191-196; Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659; and Harrington,

J.J. et al. (1997) Nat. Genet. 15:345-355.) Expression vectors derived from retroviruses, adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids, may be used for delivery of nucleotide sequences to the targeted organ, tissue, or cell population. (See, e.g., Di Nicola, M. et al. (1998) Cancer Gen. Ther. 5(6):350-356; Yu, M. et al. (1993) Proc. Natl. Acad. Sci.

5   USA 90(13):6340-6344; Buller, R.M. et al. (1985) Nature 317(6040):813-815; McGregor, D.P. et al. (1994) Mol. Immunol. 31(3):219-226; and Verma, I.M. and N. Somia (1997) Nature 389:239-242.) The invention is not limited by the host cell employed.

In bacterial systems, a number of cloning and expression vectors may be selected depending upon the use intended for polynucleotide sequences encoding XMAD. For example, routine cloning,

10   subcloning, and propagation of polynucleotide sequences encoding XMAD can be achieved using a multifunctional E. coli vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or PSPORT1 plasmid (Life Technologies). Ligation of sequences encoding XMAD into the vector's multiple cloning site disrupts the *lacZ* gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these vectors may be useful for in vitro

15   transcription, dideoxy sequencing, single strand rescue with helper phage, and creation of nested deletions in the cloned sequence. (See, e.g., Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509.) When large quantities of XMAD are needed, e.g. for the production of antibodies, vectors which direct high level expression of XMAD may be used. For example, vectors containing the strong, inducible T5 or T7 bacteriophage promoter may be used.

20   Yeast expression systems may be used for production of XMAD. A number of vectors containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH promoters, may be used in the yeast Saccharomyces cerevisiae or Pichia pastoris. In addition, such vectors direct either the secretion or intracellular retention of expressed proteins and enable integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 1995, supra;

25   Bitter, supra; and Scorer, supra.)

Plant systems may also be used for expression of XMAD. Transcription of sequences encoding XMAD may be driven viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) EMBO J. 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be

30   used. (See, e.g., Coruzzi, supra; Broglie, supra; and Winter, supra.) These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. (See, e.g., The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196.)

In mammalian cells, a number of viral-based expression systems may be utilized. In cases

35   where an adenovirus is used as an expression vector, sequences encoding XMAD may be ligated into an

30

adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain infective virus which expresses XMAD in host cells. (See, e.g., Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma

5   virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-based vectors may also be used for high-level protein expression.

Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods (liposomes, polycationic amino polymers,

10   or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355.)

For long term production of recombinant proteins in mammalian systems, stable expression of XMAD in cell lines is preferred. For example, sequences encoding XMAD can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the

15   introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

20   Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase genes, for use in *tk⁻* and *apr⁻* cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, *dhfr* confers resistance to methotrexate; *neo* confers

25   resistance to the aminoglycosides neomycin and G-418; and *als* and *pat* confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. USA 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14.) Additional selectable genes have been described, e.g., *trpB* and *hisD*, which alter cellular requirements for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan (1988) Proc. Natl. Acad. Sci. USA

30   85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins (GFP; Clontech), ß glucuronidase and its substrate ß-glucuronide, or luciferase and its substrate luciferin may be used. These markers can be used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system. (See, e.g., Rhodes, C.A. (1995) Methods Mol. Biol. 55:121-131.)

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, the presence and expression of the gene may need to be confirmed. For example, if the sequence encoding XMAD is inserted within a marker gene sequence, transformed cells containing sequences encoding XMAD can be identified by the absence of marker gene function. Alternatively, a

5   marker gene can be placed in tandem with a sequence encoding XMAD under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

In general, host cells that contain the nucleic acid sequence encoding XMAD and that express XMAD may be identified by a variety of procedures known to those of skill in the art. These

10   procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein sequences.

Immunological methods for detecting and measuring the expression of XMAD using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include

15   enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on XMAD is preferred, but a competitive binding assay may be employed. These and other assays are well known in the art. (See, e.g., Hampton, R. et al. (1990) Serological Methods, a Laboratory Manual, APS Press, St. Paul MN, Sect. IV; Coligan, J.E.

20   et al. (1997) Current Protocols in Immunology, Greene Pub. Associates and Wiley-Interscience, New York NY; and Pound, J.D. (1998) Immunochemical Protocols, Humana Press, Totowa NJ.)

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides encoding XMAD include

25   oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide. Alternatively, the sequences encoding XMAD, or any fragments thereof, may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of

30   commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega (Madison WI), and US Biochemical. Suitable reporter molecules or labels which may be used for ease of detection include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with nucleotide sequences encoding XMAD may be cultured under

32

conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a transformed cell may be secreted or retained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode XMAD may be designed to contain signal sequences which direct

5   secretion of XMAD through a prokaryotic or eukaryotic cell membrane.

In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" or "pro" form of the

10   protein may also be used to specify protein targeting, folding, and/or activity. Different host cells which have specific cellular machinery and characteristic mechanisms for post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and WI38) are available from the American Type Culture Collection (ATCC, Manassas VA) and may be chosen to ensure the correct modification and processing of the foreign protein.

15   In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences encoding XMAD may be ligated to a heterologous sequence resulting in translation of a fusion protein in any of the aforementioned host systems. For example, a chimeric XMAD protein containing a heterologous moiety that can be recognized by a commercially available antibody may facilitate the screening of peptide libraries for inhibitors of XMAD activity. Heterologous protein and

20   peptide moieties may also facilitate purification of fusion proteins using commercially available affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), maltose binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-His, FLAG, c-myc, and hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their cognate fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, calmodulin, and metal-chelate resins,

25   respectively. FLAG, c-myc, and hemagglutinin (HA) enable immunoaffinity purification of fusion proteins using commercially available monoclonal and polyclonal antibodies that specifically recognize these epitope tags. A fusion protein may also be engineered to contain a proteolytic cleavage site located between the XMAD encoding sequence and the heterologous protein sequence, so that XMAD may be cleaved away from the heterologous moiety following purification. Methods for fusion protein

30   expression and purification are discussed in Ausubel (1995, supra, ch. 10). A variety of commercially available kits may also be used to facilitate expression and purification of fusion proteins.

In a further embodiment of the invention, synthesis of radiolabeled XMAD may be achieved in vitro using the TNT rabbit reticulocyte lysate or wheat germ extract system (Promega). These systems couple transcription and translation of protein-coding sequences operably associated with the T7, T3, or

33

SP6 promoters. Translation takes place in the presence of a radiolabeled amino acid precursor, for example, ^{35}S-methionine.

XMAD of the present invention or fragments thereof may be used to screen for compounds that specifically bind to XMAD. At least one and up to a plurality of test compounds may be
5   screened for specific binding to XMAD. Examples of test compounds include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

In one embodiment, the compound thus identified is closely related to the natural ligand of XMAD, e.g., a ligand or fragment thereof, a natural substrate, a structural or functional mimetic, or a natural binding partner. (See, e.g., Coligan, J.E. et al. (1991) Current Protocols in Immunology 1(2):
10   Chapter 5.) Similarly, the compound can be closely related to the natural receptor to which XMAD binds, or to at least a fragment of the receptor, e.g., the ligand binding site. In either case, the compound can be rationally designed using known techniques. In one embodiment, screening for these compounds involves producing appropriate cells which express XMAD, either as a secreted protein or on the cell membrane. Preferred cells include cells from mammals, yeast, Drosophila, or E.
15   coli. Cells expressing XMAD or cell membrane fractions which contain XMAD are then contacted with a test compound and binding, stimulation, or inhibition of activity of either XMAD or the compound is analyzed.

An assay may simply test binding of a test compound to the polypeptide, wherein binding is detected by a fluorophore, radioisotope, enzyme conjugate, or other detectable label. For example,
20   the assay may comprise the steps of combining at least one test compound with XMAD, either in solution or affixed to a solid support, and detecting the binding of XMAD to the compound. Alternatively, the assay may detect or measure binding of a test compound in the presence of a labeled competitor. Additionally, the assay may be carried out using cell-free preparations, chemical libraries, or natural product mixtures, and the test compound(s) may be free in solution or affixed to a
25   solid support.

XMAD of the present invention or fragments thereof may be used to screen for compounds that modulate the activity of XMAD. Such compounds may include agonists, antagonists, or partial or inverse agonists. In one embodiment, an assay is performed under conditions permissive for XMAD activity, wherein XMAD is combined with at least one test compound, and the activity of
30   XMAD in the presence of a test compound is compared with the activity of XMAD in the absence of the test compound. A change in the activity of XMAD in the presence of the test compound is indicative of a compound that modulates the activity of XMAD. Alternatively, a test compound is combined with an in vitro or cell-free system comprising XMAD under conditions suitable for XMAD activity, and the assay is performed. In either of these assays, a test compound which
35   modulates the activity of XMAD may do so indirectly and need not come in direct contact with the

34

test compound. At least one and up to a plurality of test compounds may be screened.

In another embodiment, polynucleotides encoding XMAD or their mammalian homologs may be "knocked out" in an animal model system using homologous recombination in embryonic stem (ES) cells. Such techniques are well known in the art and are useful for the generation of animal

5   models of human disease. (See, e.g., U.S. Patent No. 5,175,383 and U.S. Patent No. 5,767,337.) For example, mouse ES cells, such as the mouse 129/SvJ cell line, are derived from the early mouse embryo and grown in culture. The ES cells are transformed with a vector containing the gene of interest disrupted by a marker gene, e.g., the neomycin phosphotransferase gene (neo; Capecchi, M.R. (1989) Science 244:1288-1292). The vector integrates into the corresponding region of the host

10 genome by homologous recombination. Alternatively, homologous recombination takes place using the Cre-loxP system to knockout a gene of interest in a tissue- or developmental stage-specific manner (Marth, J.D. (1996) Clin. Invest. 97:1999-2002; Wagner, K.U. et al. (1997) Nucleic Acids Res. 25:4323-4330). Transformed ES cells are identified and microinjected into mouse cell blastocysts such as those from the C57BL/6 mouse strain. The blastocysts are surgically transferred

15 to pseudopregnant dams, and the resulting chimeric progeny are genotyped and bred to produce heterozygous or homozygous strains. Transgenic animals thus generated may be tested with potential therapeutic or toxic agents.

Polynucleotides encoding XMAD may also be manipulated in vitro in ES cells derived from human blastocysts. Human ES cells have the potential to differentiate into at least eight separate cell

20 lineages including endoderm, mesoderm, and ectodermal cell types. These cell lineages differentiate into, for example, neural cells, hematopoietic lineages, and cardiomyocytes (Thomson, J.A. et al. (1998) Science 282:1145-1147).

Polynucleotides encoding XMAD can also be used to create "knockin" humanized animals (pigs) or transgenic animals (mice or rats) to model human disease. With knockin technology, a

25 region of a polynucleotide encoding XMAD is injected into animal ES cells, and the injected sequence integrates into the animal cell genome. Transformed cells are injected into blastulae, and the blastulae are implanted as described above. Transgenic progeny or inbred lines are studied and treated with potential pharmaceutical agents to obtain information on treatment of a human disease. Alternatively, a mammal inbred to overexpress XMAD, e.g., by secreting XMAD in its milk, may

30 also serve as a convenient source of that protein (Janne, J. et al. (1998) Biotechnol. Annu. Rev. 4:55-74).

THERAPEUTICS

Chemical and structural similarity, e.g., in the context of sequences and motifs, exists between regions of XMAD and extracellular matrix and cell adhesion molecules. In addition, the

35 expression of XMAD is closely associated with cell proliferation. Therefore, XMAD appears to play

a role in genetic, autoimmune/inflammation, and cell proliferative disorders, including cancer. In the treatment of disorders associated with increased XMAD expression or activity, it is desirable to decrease the expression or activity of XMAD. In the treatment of disorders associated with decreased XMAD expression or activity, it is desirable to increase the expression or activity of XMAD.

5   Therefore, in one embodiment, XMAD or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of XMAD. Examples of such disorders include, but are not limited to, a genetic disorder, such as adrenoleukodystrophy, Alport's syndrome, choroideremia, Duchenne and Becker muscular dystrophy, Down's syndrome, cystic fibrosis, chronic granulomatous disease, Gaucher's disease,

10   Huntington's chorea, Marfan's syndrome, muscular dystrophy, myotonic dystrophy, pycnodysostosis, Refsum's syndrome, retinoblastoma, sickle cell anemia, thalassemia, Werner syndrome, von Willebrand's disease, Wilms' tumor, Zellweger syndrome, peroxisomal acyl-CoA oxidase deficiency, peroxisomal thiolase deficiency, peroxisomal bifunctional protein deficiency, mitochondrial carnitine palmitoyl transferase and carnitine deficiency, mitochondrial very-long-chain acyl-CoA

15   dehydrogenase deficiency, mitochondrial medium-chain acyl-CoA dehydrogenase deficiency, mitochondrial short-chain acyl-CoA dehydrogenase deficiency, mitochondrial electron transport flavoprotein and electron transport flavoprotein:ubiquinone oxidoreductase deficiency, mitochondrial trifunctional protein deficiency, and mitochondrial short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency; an autoimmune/inflammation disorder, such as acquired immunodeficiency syndrome

20   (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis,

25   erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura,

30   ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma; and a cell proliferative disorder, such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers

35   including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma,

and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus.

In another embodiment, a vector capable of expressing XMAD or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of XMAD including, but not limited to, those described above.

In a further embodiment, a composition comprising a substantially purified XMAD in conjunction with a suitable pharmaceutical carrier may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of XMAD including, but not limited to, those provided above.

In still another embodiment, an agonist which modulates the activity of XMAD may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of XMAD including, but not limited to, those listed above.

In a further embodiment, an antagonist of XMAD may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of XMAD. Examples of such disorders include, but are not limited to, those genetic, autoimmune/inflammation, and cell proliferative disorders, including cancer, described above. In one aspect, an antibody which specifically binds XMAD may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissues which express XMAD.

In an additional embodiment, a vector expressing the complement of the polynucleotide encoding XMAD may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of XMAD including, but not limited to, those described above.

In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary sequences, or vectors of the invention may be administered in combination with other appropriate therapeutic agents. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

An antagonist of XMAD may be produced using methods which are generally known in the art. In particular, purified XMAD may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind XMAD. Antibodies to XMAD may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which inhibit

37

dimer formation) are generally preferred for therapeutic use.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans, and others may be immunized by injection with XMAD or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various adjuvants may be used to
5   increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to
10   XMAD have an amino acid sequence consisting of at least about 5 amino acids, and generally will consist of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein. Short stretches of XMAD amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

15   Monoclonal antibodies to XMAD may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (See, e.g., Kohler, G. et al. (1975) Nature 256:495-497; Kozbor, D. et al. (1985) J. Immunol. Methods 81:31-42; Cote, R.J. et al. (1983) Proc. Natl. Acad. Sci. USA 80:2026-2030; and
20   Cole, S.P. et al. (1984) Mol. Cell Biol. 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) Proc. Natl. Acad. Sci. USA 81:6851-6855; Neuberger, M.S. et al. (1984) Nature 312:604-608; and Takeda,
25   S. et al. (1985) Nature 314:452-454.) Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce XMAD-specific single chain antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g., Burton, D.R. (1991) Proc. Natl. Acad. Sci. USA 88:10134-10137.)

30   Antibodies may also be produced by inducing in vivo production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) Proc. Natl. Acad. Sci. USA 86:3833-3837; Winter, G. et al. (1991) Nature 349:293-299.)

Antibody fragments which contain specific binding sites for XMAD may also be generated.

For example, such fragments include, but are not limited to, F(ab')₂ fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the F(ab')2 fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (See, e.g., Huse, W.D. et al.

5   (1989) Science 246:1275-1281.)

Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between XMAD and its

10   specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering XMAD epitopes is generally used, but a competitive binding assay may also be employed (Pound, supra).

Various methods such as Scatchard analysis in conjunction with radioimmunoassay techniques may be used to assess the affinity of antibodies for XMAD. Affinity is expressed as an association

15   constant, K_a, which is defined as the molar concentration of XMAD-antibody complex divided by the molar concentrations of free antigen and free antibody under equilibrium conditions. The K_a determined for a preparation of polyclonal antibodies, which are heterogeneous in their affinities for multiple XMAD epitopes, represents the average affinity, or avidity, of the antibodies for XMAD. The K_a determined for a preparation of monoclonal antibodies, which are monospecific for a particular XMAD

20   epitope, represents a true measure of affinity. High-affinity antibody preparations with K_a ranging from about 10^9 to 10^{12} L/mole are preferred for use in immunoassays in which the XMAD-antibody complex must withstand rigorous manipulations. Low-affinity antibody preparations with K_a ranging from about 10^6 to 10^7 L/mole are preferred for use in immunopurification and similar procedures which ultimately require dissociation of XMAD, preferably in active form, from the antibody (Catty, D.

25   (1988) Antibodies, Volume I: A Practical Approach, IRL Press, Washington DC; Liddell, J.E. and A. Cryer (1991) A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, New York NY).

The titer and avidity of polyclonal antibody preparations may be further evaluated to determine the quality and suitability of such preparations for certain downstream applications. For example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml, preferably 5-10 mg

30   specific antibody/ml, is generally employed in procedures requiring precipitation of XMAD-antibody complexes. Procedures for evaluating antibody specificity, titer, and avidity, and guidelines for antibody quality and usage in various applications, are generally available. (See, e.g., Catty, supra, and Coligan et al., supra.)

In another embodiment of the invention, the polynucleotides encoding XMAD, or any fragment

or complement thereof, may be used for therapeutic purposes. In one aspect, modifications of gene expression can be achieved by designing complementary sequences or antisense molecules (DNA, RNA, PNA, or modified oligonucleotides) to the coding or regulatory regions of the gene encoding XMAD. Such technology is well known in the art, and antisense oligonucleotides or larger fragments can be

5   designed from various locations along the coding or control regions of sequences encoding XMAD. (See, e.g., Agrawal, S., ed. (1996) Antisense Therapeutics, Humana Press Inc., Totawa NJ.)

In therapeutic use, any gene delivery system suitable for introduction of the antisense sequences into appropriate target cells can be used. Antisense sequences can be delivered intracellularly in the form of an expression plasmid which, upon transcription, produces a sequence

10   complementary to at least a portion of the cellular sequence encoding the target protein. (See, e.g., Slater, J.E. et al. (1998) J. Allergy Clin. Immunol. 102(3):469-475; and Scanlon, K.J. et al. (1995) 9(13):1288-1296.) Antisense sequences can also be introduced intracellularly through the use of viral vectors, such as retrovirus and adeno-associated virus vectors. (See, e.g., Miller, A.D. (1990) Blood 76:271; Ausubel, supra; Uckert, W. and W. Walther (1994) Pharmacol. Ther. 63(3):323-347.) Other

15   gene delivery mechanisms include liposome-derived systems, artificial viral envelopes, and other systems known in the art. (See, e.g., Rossi, J.J. (1995) Br. Med. Bull. 51(1):217-225; Boado, R.J. et al. (1998) J. Pharm. Sci. 87(11):1308-1315; and Morris, M.C. et al. (1997) Nucleic Acids Res. 25(14):2730-2736.)

In another embodiment of the invention, polynucleotides encoding XMAD may be used for

20   somatic or germline gene therapy. Gene therapy may be performed to (i) correct a genetic deficiency (e.g., in the cases of severe combined immunodeficiency (SCID)-X1 disease characterized by X-linked inheritance (Cavazzana-Calvo, M. et al. (2000) Science 288:669-672), severe combined immunodeficiency syndrome associated with an inherited adenosine deaminase (ADA) deficiency (Blaese, R.M. et al. (1995) Science 270:475-480; Bordignon, C. et al. (1995) Science 270:470-475),

25   cystic fibrosis (Zabner, J. et al. (1993) Cell 75:207-216; Crystal, R.G. et al. (1995) Hum. Gene Therapy 6:643-666; Crystal, R.G. et al. (1995) Hum. Gene Therapy 6:667-703), thalassamias, familial hypercholesterolemia, and hemophilia resulting from Factor VIII or Factor IX deficiencies (Crystal, R.G. (1995) Science 270:404-410; Verma, I.M. and N. Somia (1997) Nature 389:239-242)), (ii) express a conditionally lethal gene product (e.g., in the case of cancers which result from unregulated

30   cell proliferation), or (iii) express a protein which affords protection against intracellular parasites (e.g., against human retroviruses, such as human immunodeficiency virus (HIV) (Baltimore, D. (1988) Nature 335:395-396; Poeschla, E. et al. (1996) Proc. Natl. Acad. Sci. USA. 93:11395-11399), hepatitis B or C virus (HBV, HCV); fungal parasites, such as Candida albicans and Paracoccidioides brasiliensis; and protozoan parasites such as Plasmodium falciparum and Trypanosoma cruzi). In the

35   case where a genetic deficiency in XMAD expression or regulation causes disease, the expression of

XMAD from an appropriate population of transduced cells may alleviate the clinical manifestations caused by the genetic deficiency.

In a further embodiment of the invention, diseases or disorders caused by deficiencies in XMAD are treated by constructing mammalian expression vectors encoding XMAD and introducing 5   these vectors by mechanical means into XMAD-deficient cells. Mechanical transfer technologies for use with cells in vivo or ex vitro include (i) direct DNA microinjection into individual cells, (ii) ballistic gold particle delivery, (iii) liposome-mediated transfection, (iv) receptor-mediated gene transfer, and (v) the use of DNA transposons (Morgan, R.A. and W.F. Anderson (1993) Annu. Rev. Biochem. 62:191-217; Ivics, Z. (1997) Cell 91:501-510; Boulay, J-L. and H. Récipon (1998) Curr. Opin. Biotechnol. 10   9:445-450).

Expression vectors that may be effective for the expression of XMAD include, but are not limited to, the PCDNA 3.1, EPITAG, PRCCMV2, PREP, PVAX vectors (Invitrogen, Carlsbad CA), PCMV-SCRIPT, PCMV-TAG, PEGSH/PERV (Stratagene, La Jolla CA), and PTET-OFF, PTET-ON, PTRE2, PTRE2-LUC, PTK-HYG (Clontech, Palo Alto CA). XMAD may be expressed 15   using (i) a constitutively active promoter, (e.g., from cytomegalovirus (CMV), Rous sarcoma virus (RSV), SV40 virus, thymidine kinase (TK), or β-actin genes), (ii) an inducible promoter (e.g., the tetracycline-regulated promoter (Gossen, M. and H. Bujard (1992) Proc. Natl. Acad. Sci. USA 89:5547-5551; Gossen, M. et al. (1995) Science 268:1766-1769; Rossi, F.M.V. and H.M. Blau (1998) Curr. Opin. Biotechnol. 9:451-456), commercially available in the T-REX plasmid (Invitrogen)); the 20   ecdysone-inducible promoter (available in the plasmids PVGRXR and PIND; Invitrogen); the FK506/rapamycin inducible promoter; or the RU486/mifepristone inducible promoter (Rossi, F.M.V. and H.M. Blau, supra)), or (iii) a tissue-specific promoter or the native promoter of the endogenous gene encoding XMAD from a normal individual.

Commercially available liposome transformation kits (e.g., the PERFECT LIPID 25   TRANSFECTION KIT, available from Invitrogen) allow one with ordinary skill in the art to deliver polynucleotides to target cells in culture and require minimal effort to optimize experimental parameters. In the alternative, transformation is performed using the calcium phosphate method (Graham, F.L. and A.J. Eb (1973) Virology 52:456-467), or by electroporation (Neumann, E. et al. (1982) EMBO J. 1:841-845). The introduction of DNA to primary cells requires modification of these 30   standardized mammalian transfection protocols.

In another embodiment of the invention, diseases or disorders caused by genetic defects with respect to XMAD expression are treated by constructing a retrovirus vector consisting of (i) the polynucleotide encoding XMAD under the control of an independent promoter or the retrovirus long terminal repeat (LTR) promoter, (ii) appropriate RNA packaging signals, and (iii) a Rev-responsive

element (RRE) along with additional retrovirus *cis*-acting RNA sequences and coding sequences required for efficient vector propagation. Retrovirus vectors (e.g., PFB and PFBNEO) are commercially available (Stratagene) and are based on published data (Riviere, I. et al. (1995) Proc. Natl. Acad. Sci. USA 92:6733-6737), incorporated by reference herein. The vector is propagated in an

5   appropriate vector producing cell line (VPCL) that expresses an envelope gene with a tropism for receptors on the target cells or a promiscuous envelope protein such as VSVg (Armentano, D. et al. (1987) J. Virol. 61:1647-1650; Bender, M.A. et al. (1987) J. Virol. 61:1639-1646; Adam, M.A. and A.D. Miller (1988) J. Virol. 62:3802-3806; Dull, T. et al. (1998) J. Virol. 72:8463-8471; Zufferey, R. et al. (1998) J. Virol. 72:9873-9880). U.S. Patent Number 5,910,434 to Rigg ("Method for obtaining

10 retrovirus packaging cell lines producing high transducing efficiency retroviral supernatant") discloses a method for obtaining retrovirus packaging cell lines and is hereby incorporated by reference. Propagation of retrovirus vectors, transduction of a population of cells (e.g., CD4$^+$ T-cells), and the return of transduced cells to a patient are procedures well known to persons skilled in the art of gene therapy and have been well documented (Ranga, U. et al. (1997) J. Virol. 71:7020-7029; Bauer, G. et

15 al. (1997) Blood 89:2259-2267; Bonyhadi, M.L. (1997) J. Virol. 71:4707-4716; Ranga, U. et al. (1998) Proc. Natl. Acad. Sci. USA 95:1201-1206; Su, L. (1997) Blood 89:2283-2290).

        In the alternative, an adenovirus-based gene therapy delivery system is used to deliver polynucleotides encoding XMAD to cells which have one or more genetic abnormalities with respect to the expression of XMAD. The construction and packaging of adenovirus-based vectors are well known

20 to those with ordinary skill in the art. Replication defective adenovirus vectors have proven to be versatile for importing genes encoding immunoregulatory proteins into intact islets in the pancreas (Csete, M.E. et al. (1995) Transplantation 27:263-268). Potentially useful adenoviral vectors are described in U.S. Patent Number 5,707,618 to Armentano ("Adenovirus vectors for gene therapy"), hereby incorporated by reference. For adenoviral vectors, see also Antinozzi, P.A. et al. (1999) Annu.

25 Rev. Nutr. 19:511-544; and Verma, I.M. and N. Somia (1997) Nature 18:389:239-242, both incorporated by reference herein.

        In another alternative, a herpes-based, gene therapy delivery system is used to deliver polynucleotides encoding XMAD to target cells which have one or more genetic abnormalities with respect to the expression of XMAD. The use of herpes simplex virus (HSV)-based vectors may be

30 especially valuable for introducing XMAD to cells of the central nervous system, for which HSV has a tropism. The construction and packaging of herpes-based vectors are well known to those with ordinary skill in the art. A replication-competent herpes simplex virus (HSV) type 1-based vector has been used to deliver a reporter gene to the eyes of primates (Liu, X. et al. (1999) Exp. Eye Res.169:385-395). The construction of a HSV-1 virus vector has also been disclosed in detail in U.S.

Patent Number 5,804,413 to DeLuca ("Herpes simplex virus strains for gene transfer"), which is hereby incorporated by reference. U.S. Patent Number 5,804,413 teaches the use of recombinant HSV d92 which consists of a genome containing at least one exogenous gene to be transferred to a cell under the control of the appropriate promoter for purposes including human gene therapy. Also taught by this

5 patent are the construction and use of recombinant HSV strains deleted for ICP4, ICP27 and ICP22. For HSV vectors, see also Goins, W.F. et al. (1999) J. Virol. 73:519-532 and Xu, H. et al. (1994) Dev. Biol. 163:152-161, hereby incorporated by reference. The manipulation of cloned herpesvirus sequences, the generation of recombinant virus following the transfection of multiple plasmids containing different segments of the large herpesvirus genomes, the growth and propagation of

10 herpesvirus, and the infection of cells with herpesvirus are techniques well known to those of ordinary skill in the art.

In another alternative, an alphavirus (positive, single-stranded RNA virus) vector is used to deliver polynucleotides encoding XMAD to target cells. The biology of the prototypic alphavirus, Semliki Forest Virus (SFV), has been studied extensively and gene transfer vectors have been based on

15 the SFV genome (Garoff, H. and K.-J. Li (1998) Curr. Opin. Biotechnol. 9:464-469). During alphavirus RNA replication, a subgenomic RNA is generated that normally encodes the viral capsid proteins. This subgenomic RNA replicates to higher levels than the full-length genomic RNA, resulting in the overproduction of capsid proteins relative to the viral proteins with enzymatic activity (e.g., protease and polymerase). Similarly, inserting the coding sequence for XMAD into the alphavirus

20 genome in place of the capsid-coding region results in the production of a large number of XMAD-coding RNAs and the synthesis of high levels of XMAD in vector transduced cells. While alphavirus infection is typically associated with cell lysis within a few days, the ability to establish a persistent infection in hamster normal kidney cells (BHK-21) with a variant of Sindbis virus (SIN) indicates that the lytic replication of alphaviruses can be altered to suit the needs of the gene therapy application

25 (Dryga, S.A. et al. (1997) Virology 228:74-83). The wide host range of alphaviruses will allow the introduction of XMAD into a variety of cell types. The specific transduction of a subset of cells in a population may require the sorting of cells prior to transduction. The methods of manipulating infectious cDNA clones of alphaviruses, performing alphavirus cDNA and RNA transfections, and performing alphavirus infections, are well known to those with ordinary skill in the art.

30   Oligonucleotides derived from the transcription initiation site, e.g., between about positions -10 and +10 from the start site, may also be employed to inhibit gene expression. Similarly, inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have

been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber, B.E. and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing, Mt. Kisco NY, pp. 163-177.) A complementary sequence or antisense molecule may also be designed to block translation of mRNA by preventing the transcript from binding to ribosomes.

5   Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. For example, engineered hammerhead motif ribozyme molecules may specifically and efficiently catalyze endonucleolytic cleavage of sequences encoding XMAD.

10   Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides, corresponding to the region of the target gene containing the cleavage site, may be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of

15   candidate targets may also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared by any method known in the art for the synthesis of nucleic acid molecules. These include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis.

20   Alternatively, RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding XMAD. Such DNA sequences may be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, these cDNA constructs that synthesize complementary RNA, constitutively or inducibly, can be introduced into cell lines, cells, or tissues.

25   RNA molecules may be modified to increase intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PNAs and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine, and

30   wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine which are not as easily recognized by endogenous endonucleases.

An additional embodiment of the invention encompasses a method for screening for a compound which is effective in altering expression of a polynucleotide encoding XMAD. Compounds which may be effective in altering expression of a specific polynucleotide may include,

35   but are not limited to, oligonucleotides, antisense oligonucleotides, triple helix-forming

44

oligonucleotides, transcription factors and other polypeptide transcriptional regulators, and non-macromolecular chemical entities which are capable of interacting with specific polynucleotide sequences. Effective compounds may alter polynucleotide expression by acting as either inhibitors or promoters of polynucleotide expression. Thus, in the treatment of disorders associated with increased

5   XMAD expression or activity, a compound which specifically inhibits expression of the polynucleotide encoding XMAD may be therapeutically useful, and in the treament of disorders associated with decreased XMAD expression or activity, a compound which specifically promotes expression of the polynucleotide encoding XMAD may be therapeutically useful.

        At least one, and up to a plurality, of test compounds may be screened for effectiveness in

10   altering expression of a specific polynucleotide. A test compound may be obtained by any method commonly known in the art, including chemical modification of a compound known to be effective in altering polynucleotide expression; selection from an existing, commercially-available or proprietary library of naturally-occurring or non-natural chemical compounds; rational design of a compound based on chemical and/or structural properties of the target polynucleotide; and selection from a

15   library of chemical compounds created combinatorially or randomly. A sample comprising a polynucleotide encoding XMAD is exposed to at least one test compound thus obtained. The sample may comprise, for example, an intact or permeabilized cell, or an in vitro cell-free or reconstituted biochemical system. Alterations in the expression of a polynucleotide encoding XMAD are assayed by any method commonly known in the art. Typically, the expression of a specific nucleotide is

20   detected by hybridization with a probe having a nucleotide sequence complementary to the sequence of the polynucleotide encoding XMAD. The amount of hybridization may be quantified, thus forming the basis for a comparison of the expression of the polynucleotide both with and without exposure to one or more test compounds. Detection of a change in the expression of a polynucleotide exposed to a test compound indicates that the test compound is effective in altering the expression of

25   the polynucleotide. A screen for a compound effective in altering expression of a specific polynucleotide can be carried out, for example, using a Schizosaccharomyces pombe gene expression system (Atkins, D. et al. (1999) U.S. Patent No. 5,932,435; Arndt, G.M. et al. (2000) Nucleic Acids Res. 28:E15) or a human cell line such as HeLa cell (Clarke, M.L. et al. (2000) Biochem. Biophys. Res. Commun. 268:8-13). A particular embodiment of the present invention involves screening a

30   combinatorial library of oligonucleotides (such as deoxyribonucleotides, ribonucleotides, peptide nucleic acids, and modified oligonucleotides) for antisense activity against a specific polynucleotide sequence (Bruice, T.W. et al. (1997) U.S. Patent No. 5,686,242; Bruice, T.W. et al. (2000) U.S. Patent No. 6,022,691).

        Many methods for introducing vectors into cells or tissues are available and equally suitable for

35   use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken

from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nat. Biotechnol. 15:462-466.)

5   Any of the therapeutic methods described above may be applied to any subject in need of such therapy, including, for example, mammals such as humans, dogs, cats, cows, horses, rabbits, and monkeys.

           An additional embodiment of the invention relates to the administration of a composition which generally comprises an active ingredient formulated with a pharmaceutically acceptable excipient.

10   Excipients may include, for example, sugars, starches, celluloses, gums, and proteins. Various formulations are commonly known and are thoroughly discussed in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing, Easton PA). Such compositions may consist of XMAD, antibodies to XMAD, and mimetics, agonists, antagonists, or inhibitors of XMAD.

           The compositions utilized in this invention may be administered by any number of routes

15   including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, pulmonary, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

           Compositions for pulmonary administration may be prepared in liquid or dry powder form. These compositions are generally aerosolized immediately prior to inhalation by the patient. In the case

20   of small molecules (e.g. traditional low molecular weight organic drugs), aerosol delivery of fast-acting formulations is well-known in the art. In the case of macromolecules (e.g. larger peptides and proteins), recent developments in the field of pulmonary delivery via the alveolar region of the lung have enabled the practical delivery of drugs such as insulin to blood circulation (see, e.g., Patton, J.S. et al., U.S. Patent No. 5,997,848). Pulmonary delivery has the advantage of administration without needle

25   injection, and obviates the need for potentially toxic penetration enhancers.

           Compositions suitable for use in the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

           Specialized forms of compositions may be prepared for direct intracellular delivery of

30   macromolecules comprising XMAD or fragments thereof. For example, liposome preparations containing a cell-impermeable macromolecule may promote cell fusion and intracellular delivery of the macromolecule. Alternatively, XMAD or a fragment thereof may be joined to a short cationic N-terminal portion from the HIV Tat-1 protein. Fusion proteins thus generated have been found to transduce into the cells of all tissues, including the brain, in a mouse model system (Schwarze, S.R. et

al. (1999) Science 285:1569-1572).

For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells, or in animal models such as mice, rats, rabbits, dogs, monkeys, or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, for example XMAD or fragments thereof, antibodies of XMAD, and agonists, antagonists or inhibitors of XMAD, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by calculating the ED_{50} (the dose therapeutically effective in 50% of the population) or LD_{50} (the dose lethal to 50% of the population) statistics. The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as the LD_{50}/ED_{50} ratio. Compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used to formulate a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that includes the ED_{50} with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

The exact dosage will be determined by the practitioner, in light of factors related to the subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the active moiety or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, the general health of the subject, the age, weight, and gender of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. Long-acting compositions may be administered every 3 to 4 days, every week, or biweekly depending on the half-life and clearance rate of the particular formulation.

Normal dosage amounts may vary from about 0.1 μg to 100,000 μg, up to a total dose of about 1 gram, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

DIAGNOSTICS

In another embodiment, antibodies which specifically bind XMAD may be used for the diagnosis of disorders characterized by expression of XMAD, or in assays to monitor patients being

47

treated with XMAD or agonists, antagonists, or inhibitors of XMAD. Antibodies useful for diagnostic purposes may be prepared in the same manner as described above for therapeutics. Diagnostic assays for XMAD include methods which utilize the antibody and a label to detect XMAD in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and

5   may be labeled by covalent or non-covalent attachment of a reporter molecule. A wide variety of reporter molecules, several of which are described above, are known in the art and may be used.

A variety of protocols for measuring XMAD, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of XMAD expression. Normal or standard values for XMAD expression are established by combining body fluids or cell extracts

10   taken from normal mammalian subjects, for example, human subjects, with antibody to XMAD under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, such as photometric means. Quantities of XMAD expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

15   In another embodiment of the invention, the polynucleotides encoding XMAD may be used for diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantify gene expression in biopsied tissues in which expression of XMAD may be correlated with disease. The diagnostic assay may be used to determine absence, presence, and excess expression of

20   XMAD, and to monitor regulation of XMAD levels during therapeutic intervention.

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding XMAD or closely related molecules may be used to identify nucleic acid sequences which encode XMAD. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a

25   conserved motif, and the stringency of the hybridization or amplification will determine whether the probe identifies only naturally occurring sequences encoding XMAD, allelic variants, or related sequences.

Probes may also be used for the detection of related sequences, and may have at least 50% sequence identity to any of the XMAD encoding sequences. The hybridization probes of the subject

30   invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:22-42 or from genomic sequences including promoters, enhancers, and introns of the XMAD gene.

Means for producing specific hybridization probes for DNAs encoding XMAD include the cloning of polynucleotide sequences encoding XMAD or XMAD derivatives into vectors for the production of mRNA probes. Such vectors are known in the art, are commercially available, and may

be used to synthesize RNA probes in vitro by means of the addition of the appropriate RNA
polymerases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a variety
of reporter groups, for example, by radionuclides such as ^{32}P or ^{35}S, or by enzymatic labels, such as
alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

5   Polynucleotide sequences encoding XMAD may be used for the diagnosis of disorders
associated with expression of XMAD. Examples of such disorders include, but are not limited to, a
genetic disorder, such as adrenoleukodystrophy, Alport's syndrome, choroideremia, Duchenne and
Becker muscular dystrophy, Down's syndrome, cystic fibrosis, chronic granulomatous disease,
Gaucher's disease, Huntington's chorea, Marfan's syndrome, muscular dystrophy, myotonic

10   dystrophy, pycnodysostosis, Refsum's syndrome, retinoblastoma, sickle cell anemia, thalassemia,
Werner syndrome, von Willebrand's disease, Wilms' tumor, Zellweger syndrome, peroxisomal acyl-
CoA oxidase deficiency, peroxisomal thiolase deficiency, peroxisomal bifunctional protein
deficiency, mitochondrial carnitine palmitoyl transferase and carnitine deficiency, mitochondrial very-
long-chain acyl-CoA dehydrogenase deficiency, mitochondrial medium-chain acyl-CoA

15   dehydrogenase deficiency, mitochondrial short-chain acyl-CoA dehydrogenase deficiency,
mitochondrial electron transport flavoprotein and electron transport flavoprotein:ubiquinone
oxidoreductase deficiency, mitochondrial trifunctional protein deficiency, and mitochondrial short-
chain 3-hydroxyacyl-CoA dehydrogenase deficiency; an autoimmune/inflammation disorder, such as
acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress

20   syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis,
autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-
candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's
disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia
with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis,

25   glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis,
hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or
pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's
syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic
lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner

30   syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial,
fungal, parasitic, protozoal, and helminthic infections, and trauma; and a cell proliferative disorder,
such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed
connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria,
polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma,

35   leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of

the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus. The polynucleotide sequences encoding XMAD may be used in Southern or northern analysis, dot blot, or other membrane-based

5   technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered XMAD expression. Such qualitative or quantitative methods are well known in the art.

In a particular aspect, the nucleotide sequences encoding XMAD may be useful in assays that detect the presence of associated disorders, particularly those mentioned above. The nucleotide

10   sequences encoding XMAD may be labeled by standard methods and added to a fluid or tissue sample from a patient under conditions suitable for the formation of hybridization complexes. After a suitable incubation period, the sample is washed and the signal is quantified and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to a control sample then the presence of altered levels of nucleotide sequences encoding XMAD in the sample

15   indicates the presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

In order to provide a basis for the diagnosis of a disorder associated with expression of XMAD, a normal or standard profile for expression is established. This may be accomplished by combining

20   body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding XMAD, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used. Standard values obtained in this manner may be compared with values obtained from samples from

25   patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

Once the presence of a disorder is established and a treatment protocol is initiated, hybridization assays may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate that which is observed in the normal subject. The results obtained from

30   successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

With respect to cancer, the presence of an abnormal amount of transcript (either under- or overexpressed) in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual

clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Additional diagnostic uses for oligonucleotides designed from the sequences encoding XMAD

5   may involve the use of PCR. These oligomers may be chemically synthesized, generated enzymatically, or produced in vitro. Oligomers will preferably contain a fragment of a polynucleotide encoding XMAD, or a fragment of a polynucleotide complementary to the polynucleotide encoding XMAD, and will be employed under optimized conditions for identification of a specific gene or condition. Oligomers may also be employed under less stringent conditions for detection or quantification of

10   closely related DNA or RNA sequences.

In a particular aspect, oligonucleotide primers derived from the polynucleotide sequences encoding XMAD may be used to detect single nucleotide polymorphisms (SNPs). SNPs are substitutions, insertions and deletions that are a frequent cause of inherited or acquired genetic disease in humans. Methods of SNP detection include, but are not limited to, single-stranded conformation

15   polymorphism (SSCP) and fluorescent SSCP (fSSCP) methods. In SSCP, oligonucleotide primers derived from the polynucleotide sequences encoding XMAD are used to amplify DNA using the polymerase chain reaction (PCR). The DNA may be derived, for example, from diseased or normal tissue, biopsy samples, bodily fluids, and the like. SNPs in the DNA cause differences in the secondary and tertiary structures of PCR products in single-stranded form, and these differences are detectable

20   using gel electrophoresis in non-denaturing gels. In fSCCP, the oligonucleotide primers are fluorescently labeled, which allows detection of the amplimers in high-throughput equipment such as DNA sequencing machines. Additionally, sequence database analysis methods, termed in silico SNP (isSNP), are capable of identifying polymorphisms by comparing the sequence of individual overlapping DNA fragments which assemble into a common consensus sequence. These computer-

25   based methods filter out sequence variations due to laboratory preparation of DNA and sequencing errors using statistical models and automated analyses of DNA sequence chromatograms. In the alternative, SNPs may be detected and characterized by mass spectrometry using, for example, the high throughput MASSARRAY system (Sequenom, Inc., San Diego CA).

Methods which may also be used to quantify the expression of XMAD include radiolabeling or

30   biotinylating nucleotides, coamplification of a control nucleic acid, and interpolating results from standard curves. (See, e.g., Melby, P.C. et al. (1993) J. Immunol. Methods 159:235-244; Duplaa, C. et al. (1993) Anal. Biochem. 212:229-236.) The speed of quantitation of multiple samples may be accelerated by running the assay in a high-throughput format where the oligomer or polynucleotide of interest is presented in various dilutions and a spectrophotometric or colorimetric response gives rapid

quantitation.

In further embodiments, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as elements on a microarray. The microarray can be used in transcript imaging techniques which monitor the relative expression levels of large

5   numbers of genes simultaneously as described in Seilhamer, J.J. et al., "Comparative Gene Transcript Analysis," U.S. Patent No. 5,840,484, incorporated herein by reference. The microarray may also be used to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, to monitor progression/regression of disease as a function of gene expression, and to develop and monitor the

10   activities of therapeutic agents in the treatment of disease. In particular, this information may be used to develop a pharmacogenomic profile of a patient in order to select the most appropriate and effective treatment regimen for that patient. For example, therapeutic agents which are highly effective and display the fewest side effects may be selected for a patient based on his/her pharmacogenomic profile.

In another embodiment, antibodies specific for XMAD, or XMAD or fragments thereof may be

15   used as elements on a microarray. The microarray may be used to monitor or measure protein-protein interactions, drug-target interactions, and gene expression profiles, as described above.

A particular embodiment relates to the use of the polynucleotides of the present invention to generate a transcript image of a tissue or cell type. A transcript image represents the global pattern of gene expression by a particular tissue or cell type. Global gene expression patterns are analyzed by

20   quantifying the number of expressed genes and their relative abundance under given conditions and at a given time. (See Seilhamer et al., "Comparative Gene Transcript Analysis," U.S. Patent Number 5,840,484, expressly incorporated by reference herein.) Thus a transcript image may be generated by hybridizing the polynucleotides of the present invention or their complements to the totality of transcripts or reverse transcripts of a particular tissue or cell type. In one embodiment, the

25   hybridization takes place in high-throughput format, wherein the polynucleotides of the present invention or their complements comprise a subset of a plurality of elements on a microarray. The resultant transcript image would provide a profile of gene activity.

Transcript images may be generated using transcripts isolated from tissues, cell lines, biopsies, or other biological samples. The transcript image may thus reflect gene expression in vivo, as in the

30   case of a tissue or biopsy sample, or in vitro, as in the case of a cell line.

Transcript images which profile the expression of the polynucleotides of the present invention may also be used in conjunction with in vitro model systems and preclinical evaluation of pharmaceuticals, as well as toxicological testing of industrial and naturally-occurring environmental compounds. All compounds induce characteristic gene expression patterns, frequently termed

molecular fingerprints or toxicant signatures, which are indicative of mechanisms of action and toxicity (Nuwaysir, E.F. et al. (1999) Mol. Carcinog. 24:153-159; Steiner, S. and N.L. Anderson (2000) Toxicol. Lett. 112-113:467-471, expressly incorporated by reference herein). If a test compound has a signature similar to that of a compound with known toxicity, it is likely to share those toxic properties.

5   These fingerprints or signatures are most useful and refined when they contain expression information from a large number of genes and gene families. Ideally, a genome-wide measurement of expression provides the highest quality signature. Even genes whose expression is not altered by any tested compounds are important as well, as the levels of expression of these genes are used to normalize the rest of the expression data. The normalization procedure is useful for comparison of expression data

10   after treatment with different compounds. While the assignment of gene function to elements of a toxicant signature aids in interpretation of toxicity mechanisms, knowledge of gene function is not necessary for the statistical matching of signatures which leads to prediction of toxicity. (See, for example, Press Release 00-02 from the National Institute of Environmental Health Sciences, released February 29, 2000, available at http://www.niehs.nih.gov/oc/news/toxchip.htm.) Therefore, it is

15   important and desirable in toxicological screening using toxicant signatures to include all expressed gene sequences.

          In one embodiment, the toxicity of a test compound is assessed by treating a biological sample containing nucleic acids with the test compound. Nucleic acids that are expressed in the treated biological sample are hybridized with one or more probes specific to the polynucleotides of the

20   present invention, so that transcript levels corresponding to the polynucleotides of the present invention may be quantified. The transcript levels in the treated biological sample are compared with levels in an untreated biological sample. Differences in the transcript levels between the two samples are indicative of a toxic response caused by the test compound in the treated sample.

          Another particular embodiment relates to the use of the polypeptide sequences of the present

25   invention to analyze the proteome of a tissue or cell type. The term proteome refers to the global pattern of protein expression in a particular tissue or cell type. Each protein component of a proteome can be subjected individually to further analysis. Proteome expression patterns, or profiles, are analyzed by quantifying the number of expressed proteins and their relative abundance under given conditions and at a given time. A profile of a cell's proteome may thus be generated by separating and

30   analyzing the polypeptides of a particular tissue or cell type. In one embodiment, the separation is achieved using two-dimensional gel electrophoresis, in which proteins from a sample are separated by isoelectric focusing in the first dimension, and then according to molecular weight by sodium dodecyl sulfate slab gel electrophoresis in the second dimension (Steiner and Anderson, supra). The proteins are visualized in the gel as discrete and uniquely positioned spots, typically by staining the gel with an agent

35   such as Coomassie Blue or silver or fluorescent stains. The optical density of each protein spot is

generally proportional to the level of the protein in the sample. The optical densities of equivalently positioned protein spots from different samples, for example, from biological samples either treated or untreated with a test compound or therapeutic agent, are compared to identify any changes in protein spot density related to the treatment. The proteins in the spots are partially sequenced using, for

5   example, standard methods employing chemical or enzymatic cleavage followed by mass spectrometry. The identity of the protein in a spot may be determined by comparing its partial sequence, preferably of at least 5 contiguous amino acid residues, to the polypeptide sequences of the present invention. In some cases, further sequence data may be obtained for definitive protein identification.

        A proteomic profile may also be generated using antibodies specific for XMAD to quantify the

10   levels of XMAD expression. In one embodiment, the antibodies are used as elements on a microarray, and protein expression levels are quantified by exposing the microarray to the sample and detecting the levels of protein bound to each array element (Lueking, A. et al. (1999) Anal. Biochem. 270:103-111; Mendoze, L.G. et al. (1999) Biotechniques 27:778-788). Detection may be performed by a variety of methods known in the art, for example, by reacting the proteins in the sample with a thiol- or amino-

15   reactive fluorescent compound and detecting the amount of fluorescence bound at each array element.

        Toxicant signatures at the proteome level are also useful for toxicological screening, and should be analyzed in parallel with toxicant signatures at the transcript level. There is a poor correlation between transcript and protein abundances for some proteins in some tissues (Anderson, N.L. and J. Seilhamer (1997) Electrophoresis 18:533-537), so proteome toxicant signatures may be useful in the

20   analysis of compounds which do not significantly affect the transcript image, but which alter the proteomic profile. In addition, the analysis of transcripts in body fluids is difficult, due to rapid degradation of mRNA, so proteomic profiling may be more reliable and informative in such cases.

        In another embodiment, the toxicity of a test compound is assessed by treating a biological sample containing proteins with the test compound. Proteins that are expressed in the treated biological

25   sample are separated so that the amount of each protein can be quantified. The amount of each protein is compared to the amount of the corresponding protein in an untreated biological sample. A difference in the amount of protein between the two samples is indicative of a toxic response to the test compound in the treated sample. Individual proteins are identified by sequencing the amino acid residues of the individual proteins and comparing these partial sequences to the polypeptides of the present invention.

30   In another embodiment, the toxicity of a test compound is assessed by treating a biological sample containing proteins with the test compound. Proteins from the biological sample are incubated with antibodies specific to the polypeptides of the present invention. The amount of protein recognized by the antibodies is quantified. The amount of protein in the treated biological sample is compared with the amount in an untreated biological sample. A difference in the amount of protein between the two

54

samples is indicative of a toxic response to the test compound in the treated sample.

Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g., Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) Proc. Natl. Acad. Sci. USA 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al.

5   (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) Proc. Natl. Acad. Sci. USA 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.) Various types of microarrays are well known and thoroughly described in DNA Microarrays: A Practical Approach, M. Schena, ed. (1999) Oxford University Press, London, hereby expressly incorporated by reference.

In another embodiment of the invention, nucleic acid sequences encoding XMAD may be used

10   to generate hybridization probes useful in mapping the naturally occurring genomic sequence. Either coding or noncoding sequences may be used, and in some instances, noncoding sequences may be preferable over coding sequences. For example, conservation of a coding sequence among members of a multi-gene family may potentially cause undesired cross hybridization during chromosomal mapping. The sequences may be mapped to a particular chromosome, to a specific region of a

15   chromosome, or to artificial chromosome constructions, e.g., human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355; Price, C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.) Once mapped, the nucleic acid sequences of the invention may be used to develop genetic

20   linkage maps, for example, which correlate the inheritance of a disease state with the inheritance of a particular chromosome region or restriction fragment length polymorphism (RFLP). (See, e.g., Lander, E.S. and D. Botstein (1986) Proc. Natl. Acad. Sci. USA 83:7353-7357.)

Fluorescent in situ hybridization (FISH) may be correlated with other physical and genetic map data. (See, e.g., Heinz-Ulrich, et al. (1995) in Meyers, supra, pp. 965-968.) Examples of genetic map

25   data can be found in various scientific journals or at the Online Mendelian Inheritance in Man (OMIM) World Wide Web site. Correlation between the location of the gene encoding XMAD on a physical map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder and thus may further positional cloning efforts.

In situ hybridization of chromosomal preparations and physical mapping techniques, such as

30   linkage analysis using established chromosomal markers, may be used for extending genetic maps. Often the placement of a gene on the chromosome of another mammalian species, such as mouse, may reveal associated markers even if the exact chromosomal locus is not known. This information is valuable to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the gene or genes responsible for a disease or syndrome have been crudely localized

35   by genetic linkage to a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences

mapping to that area may represent associated or regulatory genes for further investigation. (See, e.g., Gatti, R.A. et al. (1988) Nature 336:577-580.) The nucleotide sequence of the instant invention may also be used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

5   In another embodiment of the invention, XMAD, its catalytic or immunogenic fragments, or oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between XMAD and the agent being tested may be measured.

10   Another technique for drug screening provides for high throughput screening of compounds having suitable binding affinity to the protein of interest. (See, e.g., Geysen, et al. (1984) PCT application WO84/03564.) In this method, large numbers of different small test compounds are synthesized on a solid substrate. The test compounds are reacted with XMAD, or fragments thereof, and washed. Bound XMAD is then detected by methods well known in the art. Purified XMAD can

15   also be coated directly onto plates for use in the aforementioned drug screening techniques. Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

           In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding XMAD specifically compete with a test compound for binding XMAD.

20   In this manner, antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with XMAD.

           In additional embodiments, the nucleotide sequences which encode XMAD may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including, but not limited to, such

25   properties as the triplet genetic code and specific base pair interactions.

           Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

30   Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

           The disclosures of all patents, applications, and publications mentioned above and below, in

35   particular U.S. Ser. No. 60/172,354, and U.S. Ser. No. 60/172,852, are hereby expressly incorporated

by reference.

EXAMPLES

5   **I.   Construction of cDNA Libraries**

RNA was purchased from Clontech or isolated from tissues described in Table 4. Some tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life Technologies), a monophasic solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl

10   cushions or extracted with chloroform. RNA was precipitated from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA purity. In some cases, RNA was treated with DNase. For most libraries, poly(A+) RNA was isolated using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (QIAGEN,

15   Chatsworth CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates using other RNA isolation kits, e.g., the POLY(A)PURE mRNA purification kit (Ambion, Austin TX).

In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA libraries. Otherwise, cDNA was synthesized and cDNA libraries were constructed with the UNIZAP

20   vector system (Stratagene) or SUPERSCRIPT plasmid system (Life Technologies), using the recommended procedures or similar methods known in the art. (See, e.g., Ausubel, 1997, supra, units 5.1-6.6.) Reverse transcription was initiated using oligo d(T) or random primers. Synthetic oligonucleotide adapters were ligated to double stranded cDNA, and the cDNA was digested with the appropriate restriction enzyme or enzymes. For most libraries, the cDNA was size-selected (300-1000

25   bp) using SEPHACRYL S1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs were ligated into compatible restriction enzyme sites of the polylinker of a suitable plasmid, e.g., PBLUESCRIPT plasmid (Stratagene), PSPORT1 plasmid (Life Technologies), pcDNA2.1 plasmid (Invitrogen, Carlsbad CA), or pINCY plasmid (Incyte Genomics, Palo Alto CA). Recombinant

30   plasmids were transformed into competent E. coli cells including XL1-Blue, XL1-BlueMRF, or SOLR from Stratagene or DH5α, DH10B, or ElectroMAX DH10B from Life Technologies.

II.   Isolation of cDNA Clones

Plasmids obtained as described in Example I were recovered from host cells by in vivo excision using the UNIZAP vector system (Stratagene) or by cell lysis. Plasmids were purified using at least

one of the following: a Magic or WIZARD Minipreps DNA purification system (Promega); an AGTC Miniprep purification kit (Edge Biosystems, Gaithersburg MD); and QIAWELL 8 Plasmid, QIAWELL 8 Plus Plasmid, QIAWELL 8 Ultra Plasmid purification systems or the R.E.A.L. PREP 96 plasmid purification kit from QIAGEN. Following precipitation, plasmids were resuspended in 0.1 ml of

5   distilled water and stored, with or without lyophilization, at 4°C.

Alternatively, plasmid DNA was amplified from host cell lysates using direct link PCR in a high-throughput format (Rao, V.B. (1994) Anal. Biochem. 216:1-14). Host cell lysis and thermal cycling steps were carried out in a single reaction mixture. Samples were processed and stored in 384-well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically using

10 PICOGREEN dye (Molecular Probes, Eugene OR) and a FLUOROSKAN II fluorescence scanner (Labsystems Oy, Helsinki, Finland).

III.   Sequencing and Analysis

Incyte cDNA recovered in plasmids as described in Example II were sequenced as follows. Sequencing reactions were processed using standard methods or high-throughput instrumentation

15 such as the ABI CATALYST 800 (Applied Biosystems) thermal cycler or the PTC-200 thermal cycler (MJ Research) in conjunction with the HYDRA microdispenser (Robbins Scientific) or the MICROLAB 2200 (Hamilton) liquid transfer system. cDNA sequencing reactions were prepared using reagents provided by Amersham Pharmacia Biotech or supplied in ABI sequencing kits such as the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Applied Biosystems).

20 Electrophoretic separation of cDNA sequencing reactions and detection of labeled polynucleotides were carried out using the MEGABACE 1000 DNA sequencing system (Molecular Dynamics); the ABI PRISM 373 or 377 sequencing system (Applied Biosystems) in conjunction with standard ABI protocols and base calling software; or other sequence analysis systems known in the art. Reading frames within the cDNA sequences were identified using standard methods (reviewed in Ausubel, 1997,

25 supra, unit 7.7). Some of the cDNA sequences were selected for extension using the techniques disclosed in Example VI.

The polynucleotide sequences derived from cDNA sequencing were assembled and analyzed using a combination of software programs which utilize algorithms well known to those skilled in the art. Table 5 summarizes the tools, programs, and algorithms used and provides applicable descriptions,

30 references, and threshold parameters. The first column of Table 5 shows the tools, programs, and algorithms used, the second column provides brief descriptions thereof, the third column presents appropriate references, all of which are incorporated by reference herein in their entirety, and the fourth column presents, where applicable, the scores, probability values, and other parameters used to evaluate the strength of a match between two sequences (the higher the score, the greater the homology between

35 two sequences). Sequences were analyzed using MACDNASIS PRO software (Hitachi Software

Engineering, South San Francisco CA) and LASERGENE software (DNASTAR). Polynucleotide and polypeptide sequence alignments were generated using the default parameters specified by the clustal algorithm as incorporated into the MEGALIGN multisequence alignment program (DNASTAR), which also calculates the percent identity between aligned sequences.

5   The polynucleotide sequences were validated by removing vector, linker, and polyA sequences and by masking ambiguous bases, using algorithms and programs based on BLAST, dynamic programing, and dinucleotide nearest neighbor analysis. The sequences were then queried against a selection of public databases such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, and BLOCKS, PRINTS, DOMO, PRODOM, and PFAM to acquire annotation

10   using programs based on BLAST, FASTA, and BLIMPS. The sequences were assembled into full length polynucleotide sequences using programs based on Phred, Phrap, and Consed, and were screened for open reading frames using programs based on GeneMark, BLAST, and FASTA. The full length polynucleotide sequences were translated to derive the corresponding full length amino acid sequences, and these full length sequences were subsequently analyzed by querying against databases such as the

15   GenBank databases (described above), SwissProt, BLOCKS, PRINTS, DOMO, PRODOM, Prosite, and Hidden Markov Model (HMM)-based protein family databases such as PFAM. HMM is a probabilistic approach which analyzes consensus primary structures of gene families. (See, e.g., Eddy, S.R. (1996) Curr. Opin. Struct. Biol. 6:361-365.)

The programs described above for the assembly and analysis of full length polynucleotide and

20   amino acid sequences were also used to identify polynucleotide sequence fragments from SEQ ID NO:22-42. Fragments from about 20 to about 4000 nucleotides which are useful in hybridization and amplification technologies were described in The Invention section above.

IV.   Analysis of Polynucleotide Expression

Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene

25   and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, supra, ch. 7; Ausubel, 1995, supra, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in cDNA databases such as GenBank or LIFESEQ (Incyte Genomics). This analysis is

30   much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score, which is defined as:

$$\frac{\text{BLAST Score x Percent Identity}}{5 \text{ x minimum \{length(Seq. 1), length(Seq. 2)\}}}$$

The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. The product score is a normalized value between 0 and 100, and is calculated as follows: the BLAST score is multiplied by the percent nucleotide identity and the product is divided

5   by (5 times the length of the shorter of the two sequences). The BLAST score is calculated by assigning a score of +5 for every base that matches in a high-scoring segment pair (HSP), and -4 for every mismatch. Two sequences may share more than one HSP (separated by gaps). If there is more than one HSP, then the pair with the highest BLAST score is used to calculate the product score. The product score represents a balance between fractional overlap and quality in a BLAST alignment. For

10 example, a product score of 100 is produced only for 100% identity over the entire length of the shorter of the two sequences being compared. A product score of 70 is produced either by 100% identity and 70% overlap at one end, or by 88% identity and 100% overlap at the other. A product score of 50 is produced either by 100% identity and 50% overlap at one end, or 79% identity and 100% overlap.

The results of northern analyses are reported as a percentage distribution of libraries in which

15 the transcript encoding XMAD occurred. Analysis involved the categorization of cDNA libraries by organ/tissue and disease. The organ/tissue categories included cardiovascular, dermatologic, developmental, endocrine, gastrointestinal, hematopoietic/immune, musculoskeletal, nervous, reproductive, and urologic. The disease/condition categories included cancer, inflammation, trauma, cell proliferation, neurological, and pooled. For each category, the number of libraries expressing the

20 sequence of interest was counted and divided by the total number of libraries across all categories. Percentage values of tissue-specific and disease- or condition-specific expression are reported in Table 3.

V.   Chromosomal Mapping of XMAD Encoding Polynucleotides

The cDNA sequences which were used to assemble SEQ ID NO:22-42 were compared with

25 sequences from the Incyte LIFESEQ database and public domain databases using BLAST and other implementations of the Smith-Waterman algorithm. Sequences from these databases that matched SEQ ID NO:22-42 were assembled into clusters of contiguous and overlapping sequences using assembly algorithms such as Phrap (Table 5). Radiation hybrid and genetic mapping data available from public resources such as the Stanford Human Genome Center (SHGC), Whitehead Institute for Genome

30 Research (WIGR), and Généthon were used to determine if any of the clustered sequences had been previously mapped. Inclusion of a mapped sequence in a cluster resulted in the assignment of all sequences of that cluster, including its particular SEQ ID NO:, to that map location.

The genetic map location of SEQ ID NO:18 is described in The Invention as a range, or interval, of a human chromosome. The map position of an interval, in centiMorgans, is measured

relative to the terminus of the chromosome's p-arm. (The centiMorgan (cM) is a unit of measurement based on recombination frequencies between chromosomal markers. On average, 1 cM is roughly equivalent to 1 megabase (Mb) of DNA in humans, although this can vary widely due to hot and cold spots of recombination.) The cM distances are based on genetic markers mapped by Généthon which

5   provide boundaries for radiation hybrid markers whose sequences were included in each of the clusters. Human genome maps and other resources available to the public, such as the NCBI "GeneMap'99" World Wide Web site (http://www.ncbi.nlm.nih.gov/genemap/), can be employed to determine if previously identified disease genes map within or in proximity to the intervals indicated above.

VI.   Extension of XMAD Encoding Polynucleotides

10   The full length nucleic acid sequences of SEQ ID NO:22-42 were produced by extension of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this fragment. One primer was synthesized to initiate 5' extension of the known fragment, and the other primer, to initiate 3' extension of the known fragment. The initial primers were designed using OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides

15   in length, to have a GC content of about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations was avoided.

       Selected human cDNA libraries were used to extend the sequence. If more than one extension was necessary or desired, additional or nested sets of primers were designed.

20   High fidelity amplification was obtained by PCR using methods well known in the art. PCR was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction mix contained DNA template, 200 nmol of each primer, reaction buffer containing Mg^{2+}, $(NH_4)_2SO_4$, and β-mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme (Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer

25   pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C. In the alternative, the parameters for primer pair T7 and SK+ were as follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C.

30   The concentration of DNA in each well was determined by dispensing 100 μl PICOGREEN quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE and 0.5 μl of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar, Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II (Labsystems Oy, Helsinki, Finland) to measure the fluorescence of the sample and to quantify the

concentration of DNA. A 5 μl to 10 μl aliquot of the reaction mixture was analyzed by electrophoresis on a 1 % agarose mini-gel to determine which reactions were successful in extending the sequence.

The extended nucleotides were desalted and concentrated, transferred to 384-well plates, digested with CviJI cholera virus endonuclease (Molecular Biology Research, Madison WI), and

5   sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For shotgun sequencing, the digested nucleotides were separated on low concentration (0.6 to 0.8%) agarose gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended clones were religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in restriction site overhangs,

10   and transfected into competent E. coli cells. Transformed cells were selected on antibiotic-containing media, and individual colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x carb liquid media.

The cells were lysed, and DNA was amplified by PCR using Taq DNA polymerase (Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following parameters: Step 1:

15   94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min; Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DNA recoveries were reamplified using the same conditions as described above. Samples were diluted with 20% dimethysulfoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing primers and the DYENAMIC

20   DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Applied Biosystems).

In like manner, the polynucleotide sequences of SEQ ID NO:22-42 are used to obtain 5' regulatory sequences using the procedure above, along with oligonucleotides designed for such extension, and an appropriate genomic library.

25   **VII.   Labeling and Use of Individual Hybridization Probes**

Hybridization probes derived from SEQ ID NO:22-42 are employed to screen cDNAs, genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20 base pairs, is specifically described, essentially the same procedure is used with larger nucleotide fragments. Oligonucleotides are designed using state-of-the-art software such as OLIGO 4.06 software (National

30   Biosciences) and labeled by combining 50 pmol of each oligomer, 250 μCi of [γ-^{32}P] adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase (DuPont NEN, Boston MA). The labeled oligonucleotides are substantially purified using a SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). An aliquot containing 10^7 counts per minute of the labeled probe is used in a typical membrane-based hybridization analysis of human

genomic DNA digested with one of the following endonucleases: Ase I, Bgl II, Eco RI, Pst I, Xba I, or Pvu II (DuPont NEN).

The DNA from each digest is fractionated on a 0.7% agarose gel and transferred to nylon membranes (Nytran Plus, Schleicher & Schuell, Durham NH). Hybridization is carried out for 16 hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature under conditions of up to, for example, 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate. Hybridization patterns are visualized using autoradiography or an alternative imaging means and compared.

VIII. Microarrays

The linkage or synthesis of array elements upon a microarray can be achieved utilizing photolithography, piezoelectric printing (ink-jet printing, See, e.g., Baldeschweiler, supra), mechanical microspotting technologies, and derivatives thereof. The substrate in each of the aforementioned technologies should be uniform and solid with a non-porous surface (Schena (1999), supra). Suggested substrates include silicon, silica, glass slides, glass chips, and silicon wafers. Alternatively, a procedure analogous to a dot or slot blot may also be used to arrange and link elements to the surface of a substrate using thermal, UV, chemical, or mechanical bonding procedures. A typical array may be produced using available methods and machines well known to those of ordinary skill in the art and may contain any appropriate number of elements. (See, e.g., Schena, M. et al. (1995) Science 270:467-470; Shalon, D. et al. (1996) Genome Res. 6:639-645; Marshall, A. and J. Hodgson (1998) Nat. Biotechnol. 16:27-31.)

Full length cDNAs, Expressed Sequence Tags (ESTs), or fragments or oligomers thereof may comprise the elements of the microarray. Fragments or oligomers suitable for hybridization can be selected using software well known in the art such as LASERGENE software (DNASTAR). The array elements are hybridized with polynucleotides in a biological sample. The polynucleotides in the biological sample are conjugated to a fluorescent label or other molecular tag for ease of detection. After hybridization, nonhybridized nucleotides from the biological sample are removed, and a fluorescence scanner is used to detect hybridization at each array element. Alternatively, laser desorbtion and mass spectrometry may be used for detection of hybridization. The degree of complementarity and the relative abundance of each polynucleotide which hybridizes to an element on the microarray may be assessed. In one embodiment, microarray preparation and usage is described in detail below.

Tissue or Cell Sample Preparation

Total RNA is isolated from tissue samples using the guanidinium thiocyanate method and poly(A)$^+$ RNA is purified using the oligo-(dT) cellulose method. Each poly(A)$^+$ RNA sample is

reverse transcribed using MMLV reverse-transcriptase, 0.05 pg/μl oligo-(dT) primer (21mer), 1X first strand buffer, 0.03 units/μl RNase inhibitor, 500 μM dATP, 500 μM dGTP, 500 μM dTTP, 40 μM dCTP, 40 μM dCTP-Cy3 (BDS) or dCTP-Cy5 (Amersham Pharmacia Biotech). The reverse transcription reaction is performed in a 25 ml volume containing 200 ng poly(A)$^+$ RNA with

5   GEMBRIGHT kits (Incyte). Specific control poly(A)$^+$ RNAs are synthesized by in vitro transcription from non-coding yeast genomic DNA. After incubation at 37°C for 2 hr, each reaction sample (one with Cy3 and another with Cy5 labeling) is treated with 2.5 ml of 0.5M sodium hydroxide and incubated for 20 minutes at 85°C to the stop the reaction and degrade the RNA. Samples are purified using two successive CHROMA SPIN 30 gel filtration spin columns (CLONTECH Laboratories, Inc.

10   (CLONTECH), Palo Alto CA) and after combining, both reaction samples are ethanol precipitated using 1 ml of glycogen (1 mg/ml), 60 ml sodium acetate, and 300 ml of 100% ethanol. The sample is then dried to completion using a SpeedVAC (Savant Instruments Inc., Holbrook NY) and resuspended in 14 μl 5X SSC/0.2% SDS.

Microarray Preparation

15   Sequences of the present invention are used to generate array elements. Each array element is amplified from bacterial cells containing vectors with cloned cDNA inserts. PCR amplification uses primers complementary to the vector sequences flanking the cDNA insert. Array elements are amplified in thirty cycles of PCR from an initial quantity of 1-2 ng to a final quantity greater than 5 μg. Amplified array elements are then purified using SEPHACRYL-400 (Amersham Pharmacia

20   Biotech).

Purified array elements are immobilized on polymer-coated glass slides. Glass microscope slides (Corning) are cleaned by ultrasound in 0.1% SDS and acetone, with extensive distilled water washes between and after treatments. Glass slides are etched in 4% hydrofluoric acid (VWR Scientific Products Corporation (VWR), West Chester PA), washed extensively in distilled water, and

25   coated with 0.05% aminopropyl silane (Sigma) in 95% ethanol. Coated slides are cured in a 110°C oven.

Array elements are applied to the coated glass substrate using a procedure described in US Patent No. 5,807,522, incorporated herein by reference. 1 μl of the array element DNA, at an average concentration of 100 ng/μl, is loaded into the open capillary printing element by a high-speed robotic

30   apparatus. The apparatus then deposits about 5 nl of array element sample per slide.

Microarrays are UV-crosslinked using a STRATALINKER UV-crosslinker (Stratagene). Microarrays are washed at room temperature once in 0.2% SDS and three times in distilled water. Non-specific binding sites are blocked by incubation of microarrays in 0.2% casein in phosphate buffered saline (PBS) (Tropix, Inc., Bedford MA) for 30 minutes at 60°C followed by washes in

35   0.2% SDS and distilled water as before.

<u>Hybridization</u>

Hybridization reactions contain 9 µl of sample mixture consisting of 0.2 µg each of Cy3 and Cy5 labeled cDNA synthesis products in 5X SSC, 0.2% SDS hybridization buffer. The sample mixture is heated to 65 °C for 5 minutes and is aliquoted onto the microarray surface and covered with

5 an 1.8 cm² coverslip. The arrays are transferred to a waterproof chamber having a cavity just slightly larger than a microscope slide. The chamber is kept at 100% humidity internally by the addition of 140 µl of 5X SSC in a corner of the chamber. The chamber containing the arrays is incubated for about 6.5 hours at 60°C. The arrays are washed for 10 min at 45 °C in a first wash buffer (1X SSC, 0.1% SDS), three times for 10 minutes each at 45 °C in a second wash buffer (0.1X SSC), and dried.

10 <u>Detection</u>

Reporter-labeled hybridization complexes are detected with a microscope equipped with an Innova 70 mixed gas 10 W laser (Coherent, Inc., Santa Clara CA) capable of generating spectral lines at 488 nm for excitation of Cy3 and at 632 nm for excitation of Cy5. The excitation laser light is focused on the array using a 20X microscope objective (Nikon, Inc., Melville NY). The slide

15 containing the array is placed on a computer-controlled X-Y stage on the microscope and raster-scanned past the objective. The 1.8 cm x 1.8 cm array used in the present example is scanned with a resolution of 20 micrometers.

In two separate scans, a mixed gas multiline laser excites the two fluorophores sequentially. Emitted light is split, based on wavelength, into two photomultiplier tube detectors (PMT R1477,

20 Hamamatsu Photonics Systems, Bridgewater NJ) corresponding to the two fluorophores. Appropriate filters positioned between the array and the photomultiplier tubes are used to filter the signals. The emission maxima of the fluorophores used are 565 nm for Cy3 and 650 nm for Cy5. Each array is typically scanned twice, one scan per fluorophore using the appropriate filters at the laser source, although the apparatus is capable of recording the spectra from both fluorophores simultaneously.

25 The sensitivity of the scans is typically calibrated using the signal intensity generated by a cDNA control species added to the sample mixture at a known concentration. A specific location on the array contains a complementary DNA sequence, allowing the intensity of the signal at that location to be correlated with a weight ratio of hybridizing species of 1:100,000. When two samples from different sources (e.g., representing test and control cells), each labeled with a different

30 fluorophore, are hybridized to a single array for the purpose of identifying genes that are differentially expressed, the calibration is done by labeling samples of the calibrating cDNA with the two fluorophores and adding identical amounts of each to the hybridization mixture.

The output of the photomultiplier tube is digitized using a 12-bit RTI-835H analog-to-digital (A/D) conversion board (Analog Devices, Inc., Norwood MA) installed in an IBM-compatible PC

35 computer. The digitized data are displayed as an image where the signal intensity is mapped using a

linear 20-color transformation to a pseudocolor scale ranging from blue (low signal) to red (high signal). The data is also analyzed quantitatively. Where two different fluorophores are excited and measured simultaneously, the data are first corrected for optical crosstalk (due to overlapping emission spectra) between the fluorophores using each fluorophore's emission spectrum.

5   A grid is superimposed over the fluorescence signal image such that the signal from each spot is centered in each element of the grid. The fluorescence signal within each element is then integrated to obtain a numerical value corresponding to the average intensity of the signal. The software used for signal analysis is the GEMTOOLS gene expression analysis program (Incyte).

IX.   Complementary Polynucleotides

10   Sequences complementary to the XMAD-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring XMAD. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of XMAD. To inhibit transcription, a

15   complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the XMAD-encoding transcript.

X.   Expression of XMAD

          Expression and purification of XMAD is achieved using bacterial or virus-based expression

20   systems. For expression of XMAD in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are not limited to, the *trp-lac* (*tac*) hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the *lac* operator regulatory element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3).

25   Antibiotic resistant bacteria express XMAD upon induction with isopropyl beta-D-thiogalactopyranoside (IPTG). Expression of XMAD in eukaryotic cells is achieved by infecting insect or mammalian cell lines with recombinant Autographica californica nuclear polyhedrosis virus (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is replaced with cDNA encoding XMAD by either homologous recombination or bacterial-mediated

30   transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong polyhedrin promoter drives high levels of cDNA transcription. Recombinant baculovirus is used to infect Spodoptera frugiperda (Sf9) insect cells in most cases, or human hepatocytes, in some cases. Infection of the latter requires additional genetic modifications to baculovirus. (See Engelhard, E.K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther.

35   7:1937-1945.)

In most expression systems, XMAD is synthesized as a fusion protein with, e.g., glutathione S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step, affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-kilodalton enzyme from Schistosoma japonicum, enables the purification of fusion proteins on immobilized

5   glutathione under conditions that maintain protein activity and antigenicity (Amersham Pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from XMAD at specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Kodak). 6-His, a stretch of six consecutive histidine residues, enables purification on metal-chelate resins

10 (QIAGEN). Methods for protein expression and purification are discussed in Ausubel (1995, supra, ch. 10 and 16). Purified XMAD obtained by these methods can be used directly in the assays shown in Examples XI and XV.

XI.   Demonstration of XMAD Activity

An assay for XMAD activity measures the disruption of cytoskeletal filament networks upon

15 overexpression of XMAD in cultured cell lines. (Rezniczek, G. A. et al. (1998) J. Cell Biol. 141:209-225.) cDNA encoding XMAD is subcloned into a mammalian expression vector that drives high levels of cDNA expression. This construct is transfected into cultured cells, such as rat kangaroo PtK2 or rat bladder carcinoma 804G cells. Actin filaments and intermediate filaments such as keratin and vimentin are visualized by immunofluorescence microscopy using antibodies and techniques well known in the

20 art. The configuration and abundance of cyoskeletal filaments can be assessed and quantified using confocal imaging techniques. In particular, the bundling and collapse of cytoskeletal filament networks is indicative of XMAD activity.

Alternatively, an assay for XMAD activity measures the amount of cell aggregation induced by overexpression of XMAD. In this assay, cultured cells such as NIH3T3 are transfected with cDNA

25 encoding XMAD contained within a suitable mammalian expression vector under control of a strong promoter. Cotransfection with cDNA encoding a fluorescent marker protein, such as Green Fluorescent Protein (Clontech), is useful for identifying stable transfectants. The amount of cell agglutination, or clumping, associated with transfected cells is compared with that associated with untransfected cells. The amount of cell agglutination is a direct measure of XMAD activity.

30   Alternatively, protein kinase activity is measured by quantifying the phosphorylation of a protein substrate by XMAD in the presence of gamma-labeled ^{32}P-ATP. XMAD is incubated with the protein substrate, ^{32}P-ATP, and an appropriate kinase buffer. The ^{32}P incorporated into the substrate is separated from free ^{32}P-ATP by electrophoresis and the incorporated ^{32}P is counted using a radioisotope counter. The amount of incorporated ^{32}P is proportional to the activity of XMAD. A determination of

the specific amino acid residue phosphorylated is made by phosphoamino acid analysis of the hydrolyzed protein.

XII.   Functional Assays

XMAD function is assessed by expressing the sequences encoding XMAD at physiologically elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression vector containing a strong promoter that drives high levels of cDNA expression. Vectors of choice include pCMV SPORT plasmid (Life Technologies) and pCR3.1 plasmid (Invitrogen), both of which contain the cytomegalovirus promoter. 5-10 μg of recombinant vector are transiently transfected into a human cell line, for example, an endothelial or hematopoietic cell line, using either liposome formulations or electroporation. 1-2 μg of an additional plasmid containing sequences encoding a marker protein are co-transfected. Expression of a marker protein provides a means to distinguish transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP; Clontech), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated, laser optics-based technique, is used to identify transfected cells expressing GFP or CD64-GFP and to evaluate the apoptotic state of the cells and other cellular properties. FCM detects and quantifies the uptake of fluorescent molecules that diagnose events preceding or coincident with cell death. These events include changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in expression of cell surface and intracellular proteins as measured by reactivity with specific antibodies; and alterations in plasma membrane composition as measured by the binding of fluorescein-conjugated Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M.G. (1994) Flow Cytometry, Oxford, New York NY.

The influence of XMAD on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding XMAD and either CD64 or CD64-GFP. CD64 and CD64-GFP are expressed on the surface of transfected cells and bind to conserved regions of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art. Expression of mRNA encoding XMAD and other genes of interest can be analyzed by northern analysis or microarray techniques.

XIII.   Production of XMAD Specific Antibodies

XMAD substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) Methods Enzymol. 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

5   Alternatively, the XMAD amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, supra, ch. 11.)

10   Typically, oligopeptides of about 15 residues in length are synthesized using an ABI 431A peptide synthesizer (Applied Biosystems) using FMOC chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase immunogenicity. (See, e.g., Ausubel, 1995, supra.) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for antipeptide and anti-XMAD

15   activity by, for example, binding the peptide or XMAD to a substrate, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

XIV.   Purification of Naturally Occurring XMAD Using Specific Antibodies

Naturally occurring or recombinant XMAD is substantially purified by immunoaffinity chromatography using antibodies specific for XMAD. An immunoaffinity column is constructed by

20   covalently coupling anti-XMAD antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

Media containing XMAD are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of XMAD (e.g., high ionic strength

25   buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/XMAD binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and XMAD is collected.

XV.   Identification of Molecules Which Interact with XMAD

XMAD, or biologically active fragments thereof, are labeled with [125]I Bolton-Hunter reagent.

30   (See, e.g., Bolton A.E. and W.M. Hunter (1973) Biochem. J. 133:529-539.) Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled XMAD, washed, and any wells with labeled XMAD complex are assayed. Data obtained using different concentrations of XMAD are used to calculate values for the number, affinity, and association of XMAD with the candidate molecules.

Alternatively, molecules interacting with XMAD are analyzed using the yeast two-hybrid system as described in Fields, S. and O. Song (1989, Nature 340:245-246), or using commercially available kits based on the two-hybrid system, such as the MATCHMAKER system (Clontech).

XMAD may also be used in the PATHCALLING process (CuraGen Corp., New Haven CT)
5   which employs the yeast two-hybrid system in a high-throughput manner to determine all interactions between the proteins encoded by two large libraries of genes (Nandabalan, K. et al. (2000) U.S. Patent No. 6,057,101).

Various modifications and variations of the described methods and systems of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention.
10 Although the invention has been described in connection with certain embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within the scope of the following claims.

Table 1

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
1	22	1424691	BEPINON01	998379R1 (KIDNTUT01), 1424691H1 (BEPINON01), SXAE02538V1
2	23	1450801	PENITUT01	046316H1 (CORNNOT01), 1450801CT1 (PENITUT01), 1450801H1 (PENITUT01), 1671961H1 (BLADNOT05)
3	24	1597872	BRAINOT14	814997R1 (OVARTUT01), 814997T1 (OVARTUT01), 1412857T6 (BRAINOT12), 1438406F1 (PANCNOT08), 1597872H1 (BRAINOT14), 1797683H1 (PROSTUT05), 3346671H1 (BRAITUT24)
4	25	1674661	BLADNOT05	1655227F6 (PROSTUT08), 1674661H1 (BLADNOT05), 1675239F6 (BLADNOT05), 1879940F6 (LEUKNOT03), 2121172F6 (BRSTNOT07), 2157008F6 (BRAINOT09), 2672389F6 (KIDNNOT19), 3270393H1 (BRAINOT20), 3387668H1 (LUNGTUT17), 3685486H1 (HEAANOT01), 4103531H1 (BRSTTUT17), 4850546H1 (TESTNOT10), 5028429H1 (COLCDIT01), 5661414H1 (BRAUNOT01)
5	26	1689337	PROSTUT10	542204R1 (OVARNOT02), 961047R2 (BRSTTUT03), 1623395T6 (BRAITUT13), 1663607F6 (BRSTNOT09), 1689337H1 (PROSTUT10), 2898863R6 (THYMNON04), 3507526H1 (CONCNOT01)
6	27	1746392	STOMTUT02	682990H1 (UTRSNOT02), 1663009F6 (BRSTNOT09), 1746392H1 (STOMTUT02), 1746392T6 (STOMTUT02), 2079257F6 (ISLTNOT01), 3099537F6 (PTHYNOT03), 3111943H1 (BRSTNOT17), 3391682H1 (LUNGNOT28), 4747243F6 (SMCRUNT01)
7	28	1825182	LSUBNOT03	983441H1 (TONGTUT01), 1825182F6 (LSUBNOT03), 1825182H1 (LSUBNOT03), 1825369F6 (LSUBNOT03), SAQB00477F1, SAQB00879F1, SAQB01310F1, SAQB00187F1, SAQA02142F1, SAQA00159F1
8	29	2155541	BRAINOT09	871127T1 (LUNGAST01), 1309342R1 (COLNFET02), 1544021T1 (PROSTUT04), 2155541H1 (BRAINOT09), 2155541X15F1 (BRAINOT09)

Table 1 (Cont.)

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
9	30	2215706	SINTFET03	570718H1 (MMLR3DT01), 756160R1 (BRAITUT02), 1511501F1 (LUNGNOT14), 2215706F6 (SINTFET03), 2215706H1 (SINTFET03), 2648753F6 (OVARNOT10), 2804428H1 (PENCNOT01), 3092672T6 (BRSTNOT19), 3597972H1 (FIBPNOT01), 3604953H1 (LUNGNOT30), 3879505H1 (SPLNNOT11), 4506625F6 (OVARTDT01), 4708188H1 (BRAIFET02), 4985942H1 (LIVRTUT10), 5151981H1 (HEARFET03), 5644791H1 (UTRSTMR01), 5862219H1 (BRAYDIT01)
10	31	2347692	TESTTUT02	075856R1 (THP1PEB01), 370791R1 (LUNGNOT02), 1502478F1 (BRAITUT07), 2347692H1 (TESTTUT02), 2825041F6 (ADRETUT06)
11	32	2579048	KIDNTUT13	841019R1 (PROSTUT05), 1352253F1 (LATRTUT02), 1414589F6 (BRAINOT12), 1427648F1 (SINTBST01), 1996374R6 (BRSTTUT03), 2579048H1 (KIDNTUT13)
12	33	2604493	LUNGTUT07	901679X18 (BRSTTUT03), 927970X54R1 (BRAINOT04), 1435427F6 (PANCNOT08), 1484806F6 (CORPNOT02), 1962694T6 (BRSTNOT04), 1990921F6 (CORPNOT02), 2279985R6 (PROSNON01), 2279985T6 (PROSNON01), 2294223T6 (BRAINON01), 2604493H1 (LUNGTUT07), 2707717H1 (PONSAZT01), 3421936H1 (UCMCNOT04), 4769752H1 (BRATNOT02), 4989101H1 (LIVRTUT10), SAEA01968R1
13	34	27871082	BRSTNOT13	916228H1 (BRSTNOT04), 1251624F6 (LUNGFET03), 1440454F6 (THYRNOT03), 1664091F6 (BRSTNOT09), 1812788X17C1 (PROSTUT12), 1812788X21C1 (PROSTUT12), 2787182H1 (BRSTNOT13), 2824324F6 (ADRETUT06), 2882479T6 (UTRSTUT05), 3833543H1 (PANCNOT17), 60147041D2, 60147042B6, 60147044D2, SXAE05916V1, SXAE02927V1, g1670173
14	35	3096668	CERVNOT03	2373962F6 (ISLTNOT01), 2373962T6 (ISLTNOT01), 2762988H1 (BRSTNOT12), 3096668F6 (CERVNOT03), 3096668H1 (CERVNOT03), 3096668T6 (CERVNOT03), SCGA06156V1, SCGA11275V1, SCGA07741V1

Table 1 (Cont.)

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
15	36	3143411	HNT2AZS07	540532T6 (LNODNOT02), 852710R1 (NGANNOT01), 860567R1 (BRAITUT03), 1402106F6 (LATRTUT02), 3143411H1 (HNT2AZS07), 3143411R6 (HNT2AZS07), 5135819H1 (OVARDIT04)
16	37	3170835	BRSTNOT18	3170835H1 (BRSTNOT18), 3171275F6 (BRSTNOT18)
17	38	3550808	SYNONOT01	00101F1 (U937NOT01), 1353706T1 (LATRTUT02), 1426227F1 (SINTBST01), 1804230F6 (SINTNOT13), 2361183T6 (LUNGFET05), 2606392H1 (LUNGTUT07), 3550808H1 (SYNONOT01), SBAA00101F1
18	39	3683905	HEAANOT01	83356H1 (PROSNOT07), 1494051H1 (PROSNON01), 3683905H1 (HEAANOT01), 5512558H1 (BRADDIR01), 5700822H1 (DRGCNOT01), g1267581
19	40	4062841	BRAINOT21	1863239H1 (PROSNOT19), 1863239T6 (PROSNOT19), 4062841H1 (BRAINOT21)
20	41	6394358	UTRENOT10	875733R6 (LUNGAST01), 1312637T6 (BLADTUT02), 2296386R6 (BRSTNOT05), 2296386T6 (BRSTNOT05), 6394358H1 (UTRENOT10)
21	42	2847752		g4126329.v113.gs_6.edit.5p 1-6416; g3449297 5802-10044 5547763H1 (TESTNOC01) 8322-8532; 3373379H1 (CONNTUT05) 8722-8984; 3331371H1 (BRAIFET01) 9378-9641; 5376974H1 (BRAXNOT01) 9634-9772; 4015537F6 (BRAXNOT01) 9709-10226; 5921447H1 (BRAIFET02) 9963-10235; 4700084F6 (BRALNOT01) 10218-10739; 670937H1 (CRBLNOT01) 10517-10780; 3788576H1 (BRAHNOT05) 10608-10904; 5929111H1 (BRAIFET02) 10791- 11069; 3278762T6 (STOMFET02) 11029-11627; 2847752R6 (HNT2AZS07) 11181-11648

Table 2

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous Sequence	Analytical Methods and Databases
1 (1424691)	222	S25 T88 S155 S179 T191 T207 S90 S96 S113 S119	N7 N53 N68	M1-G29: Signal peptide E173-E181: 5-hydroxytryptamine 5A (serotonin) receptor R213-D215: Rgd cell interaction motif	g7649266 Sterile-alpha motif and leucine zipper containing kinase AZK	MOTIFS BLAST_GENBANK SPSCAN BLIMPS-PRINTS
2 (1450801)	228	S177 S99	N25	F20-G211: Leucine Rich Repeat	g3786312 Extracellular matrix protein (Nishiu, J. et al. Genomics (1998) 52:378-381)	MOTIFS BLAST_GENBANK HMMER PFAM BLIMPS-PRINTS
3 (1597872)	386	S88 S137 S229 S364 T370		G237-P247: Insulin-like growth factor G202-R341: Spliceosome-associated protein	g4033606 Extensin (Kieliszewski M.J., Lamport D.T. Plant J. (1994) 5:157-172)	MOTIFS BLAST_GENBANK BLIMPS-BLOCKS BLAST-DOMO

Table 2 (Cont.)

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous Sequence	Analytical Methods and Databases
4 (1674661)	833	S46 T276 T418 S34 T57 T229 T302 S382 T429 S505 S826 S200 S364 S480 T523 S555 T561 S685 T701 S742 Y249 Y345 Y736	N106 N121 N310 N419 N522 N564	M1-V23: Signal peptide F53-K481: Semaphorin domain	g1110599 Semaphorin homolog (Inagaki, S. et al. FEBS Lett (1995) 370:269-272)	MOTIFS BLAST_GENBANK SIGPEPT SPSCAN BLAST-PFAM
5 (1689337)	410	T358 S394 S139 S249 S17 S343 T385 S401	N3	M1-A16: Signal peptide P240-Q255: Prokaryotic molybdopterin oxidoreductase L55-A65: Prepro-orexin signature R349-D351: Rgd cell interaction motif	g3450883 Fibroin (Gosline, J.M. et al. J. Exp. Biol. (1999) 202:3295-3303)	MOTIFS BLAST_GENBANK SPSCAN BLIMPS-BLOCKS BLIMPS-PRINTS
6 (1746392)	360	S217 S255 T344 S37 S8 T28 S69 S113 T182 S188 S224 S242 S250		E17-P356: Neurofilament triplet H	g310200 proline-rich proteoglycan	MOTIFS BLAST_GENBANK BLAST-DOMO
7 (1825182)	377	S18 S41 S140 T267 S38 S62 S120 T343	N97 N128 N135 N146	F20-G211: Leucine Rich Repeat	g188864 mucin (Shimomura, T., Blood (1990) 75:2349-2356)	MOTIFS BLAST_GENBANK HMMER-PFAM BLIMPS-PRINTS

Table 2 (Cont.)

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous Sequence	Analytical Methods and Databases
8 (2155541)	182	T116		M1-F22: Signal peptide T42-D62: Neutrophil cytosol factor D170-E178: 7-fold repeat proteins I motif R60-D62: Rgd cell interaction motif	g6164953 vacuolar sorting protein VPS29 [Mus musculus] Edgar, A.J. and Polak, J.M. (2000) Biochem. Biophys. Res. Commun. 277:622-630	MOTIFS BLAST_GENBANK SPSCAN BLIMPS-PRINTS BLIMPS-PFAM
9 (2215706)	513	S239 S325 T14 S51 S71 S110 S137 S171 S208 S213 T219 S263 S268 S349 S394 S403 S404 T96 T118 S149 S239 S365 T475 S479	N69 N89 N338 N429	S94-Q108: Adrenocorticotrophin receptor S328-S335: "Phage" integrase family R196-D198: Rgd cell interaction motif	g4322670 Dentin phosphoryn P = 7.6e-07	MOTIFS BLIMPS-PRINTS BLIMPS-PFAM
10 (2347692)	361	T81 T53 S158 S257 T333 S128	N8 N51 N306 N324	G242-M268: C1q domain proteins L146-P150: Laminin G domain protein G110-P288: Fibrillar collagen carboxyl-terminus	g1562534 csdp single-stranded DNA binding protein	MOTIFS BLAST_GENBANK BLIMPS-BLOCKS BLIMPS-PFAM BLAST-DOMO
11 (2579048)	327	S18 S199 T55 T72 S73 T285 S51 S140 S177 S262	N158	K41-T55: Histone H5 signature R213-D215: Rgd cell interaction motif		MOTIFS BLIMPS_PRINTS

Table 2 (Cont.)

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous Sequence	Analytical Methods and Databases
12 (2604493)	1 110	S213 T795 S8 T17 S40 S64 S82 T118 S132 S151 S170 S192 S249 T317 T357 T476 S601 S642 S673 S674 S701 S731 T795 S1015 S1059 S1073 T84 S236 S276 T292 T309 S337 S457 T506 T744 S749 S813 T945 S976 T1078	N168 N472 N640 N671 N672 N691 N698 N729 N747 N851 N966	V532-V565, L577-F598, M609-L622: Armadillo/beta-catenin-like repeats S511-H1025: Mouse p120 protein R971-D973: Rgd cell interaction motif	g1702924 p0071 Catenin-related protein (Hatzfeld M., Nachtsheim C. J. Cell Sci. (1996) 109:2767-2778)	MOTIFS BLAST_GENBANK HMMER-PFAM BLIMPS-PFAM BLAST-PRODOM
13 (2787182)	386	S123 T210 S265 S283 S317 S326 T330 T338 T44 S79 S100 S109 T127 T142 T170 T214 S332	N14 N173	C57-Q72: Transmembrane motif M279-M363: osteonectin	g3876060 Weak similarity with nitrogen fixation regulator	MOTIFS BLAST_GENBANK HMMER PROFILESCAN
14 (3096668)	181	S114 S116 S118 S120 S122 T124 S154 T173 T13	N17	F16-E25: Alpha-type calcitonin signature	g3393011 Clumping factor B (Ni Eidhin D. et al. Mol. Microbiol. 1998 30:245-257)	MOTIFS BLAST_GENBANK BLIMPS-PRINTS

Table 2 (Cont.)

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous Sequence	Analytical Methods and Databases
15 (3143411)	374	S291 S75 S92 T206 T214 T298 T315 T23 T37 T50 S51 S262 T263 S306	N109 N304	M1-G24: Signal peptide N224-W247, V328-N348: Transmembrane motif Y46-C63, W163-C176: C-type lectin domain	g3790610 Layilin (Borowsky M.L., Hynes R.O. (1998) J. Cell Biol. 143:429-442)	MOTIFS BLAST_GENBANK SIGPEPT SPSCAN HMMER BLAST PFAM BLIMPS-PRINTS PROFILESCAN BLAST-DOMO
16 (3170835)	102	S45 T57 T44	N33	M1-T19: Signal peptide A55-103: Insect cuticle protein	g2565394 Cuticle 12	MOTIFS BLAST_GENBANK SPSCAN BLAST-PFAM PROFILESCAN BLIMPS-PRINTS BLAST-PRODOM BLAST-DOMO
17 (3550808)	510	S76 S88 S128 S150 T152 T308 T448 T461 S49 S56 S110 T138	N72 N136 N193 N253 N352 N411	M1-G20: Signal peptide L5-G23: Transmembrane motif G33-F46: Pheromone B alpha-1 receptor	g294502 Olfactomedin (Yokoe H., Anholt R.R. Proc. Natl. Acad. Sci. USA (1993) 90:4655-9)	MOTIFS BLAST_GENBANK SIGPEPT SPSCAN HMMER BLIMPS-PRINTS

Table 2 (Cont.)

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous Sequence	Analytical Methods and Databases
18 (3683905)	185	S11 S57 S173 T135		M1-L170: von Willebrand factor domain score M2-F15, R37-F51, V103-G111 M1-R171: collagen glycoprotein precursor	g2654431 Type XII collagen	MOTIFS BLAST_GENBANK HMMER-PFAM BLIMPS-PRINTS BLAST-PRODOM BLAST-DOMO
19 (4062841)	207	T83 S201 T74 S166 T174 S190		V93-T174: PDZ domain (Also known as DHR or GLGF) P91-V171: SH3 domain	g3885828 Lin-7-A (Irie M. et al. Oncogene (1999) 18:2811-2817)	MOTIFS BLAST_GENBANK HMMER-PFAM BLIMPS-PRINTS BLIMPS-PFAM BLIMPS-PRODOM BLAST-PRODOM BLAST-DOMO
20 (6394358)	238	S2 S96 S100 S12 S26 T149 S200 T203	N160	L3-A25, T64-E110, E209-R218: 7-fold repeat proteins (clathrin) R136-D138: Rgd cell interaction motif		MOTIFS BLIMPS-PFAM

Table 2 (Cont.)

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous Sequence	Analytical Methods and Databases
21	3298	S93 T307 S2706 S29 S222 S240 T266 T403 T421 T440 T457 T533 T567 T569 S658 T744 T756 T778 T831 S865 S880 T882 T931 T944 S983 T985 S1030 T1089 T1223 T1246 T1304 S1347 S1366 T1433 T1465 T1488 S1578 S1630 S1685 T1841 S1903 T2184 S2359 S2368 T2482 S2513 S2663 S2847 T2863 S2878 S2880 S2885 S2897 T2964 T2979 S2980 S3053 S3281 S186 S194 T200 T250 S409 S497 T527 S545 S833 T852 T1020 S1180 S1230 T1275 S1659 S1660 S1737 S1829 S1976 T2066 S2113 T2216 S2322 S2355 S2549 S2552 T2709 S2819 S2822 S2830 S2919 S2956 T2964 T3273 Y399 Y449 Y842 Y2299	N631 N846 N1181 N1221 N1316 N1326 N1648 N1712 N1769 N2034 N2163 N2182 N2372 N2460 N2492 N2683 N2732 N2794 N3240	L1536-Y1553 L2525-A2545 I2669-L2689 S2712-A2730 L2741-N2761: Transmembrane Domains M1-E31: signal peptide Y329-A423; Y437- L535 Y549-V641; F655- L746 Y760-T848; Y862- N952 Y965-Q1057; F1071- V1159 Y1178-I1265: Cadherin domains C1378-C1431; C1438- C1469 C1478-C1512; C1725- C1756 C1931-C1962; C1966- C2000: EGF domains F1542-D1704; F1792- E1920: Laminin G domains C2110-A2137; C2588- L2613: GPCR signature	g3449288 MEGF2 [Rattus norvegicus]	MOTIFS BLAST_GENBANK HMMER SPSCAN HMMER-PFAM BLIMPS-BLOCKS PROFILESCAN BLIMPS-PRINTS

Table 3

Polynucleotide SEQ ID NO:	Fragments	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
22	1-517 852-905	Cardiovascular (0.200) Gastrointestinal (0.200) Urologic (0.222)	Cell proliferation(0.400) Cell proliferation/Cell line (0.200) Inflammation/Trauma(0.300)	pSPORT1
23	1-2387	Reproductive (0.397) Gastrointestinal (0.132) Musculoskeletal (0.118)	Cell proliferation(0.559) Inflammation/Trauma(0.176) Other (0.118)	pINCY
24	1-901 1456-1471	Reproductive (0.262) Gastrointestinal (0.179) Nervous (0.179)	Cell proliferation(0.536) Inflammation/Trauma(0.297) Cell proliferation/Cell line (0.190)	pINCY
25	1-1928 1776-3293	Reproductive (0.294) Gastrointestinal (0.157) Nervous (0.157)	Cell proliferation(0.471) Inflammation/Trauma(0.373) Cell proliferation/Cell line (0.118)	pINCY
26	1-821 1312-1324	Reproductive (0.351) Hematopoietic/Immune (0.135) Nervous (0.135)	Cell proliferation(0.486) Cell proliferation/Cell line (0.243) Inflammation/Trauma (0.351)	pINCY
27	1-626 1034-1324	Reproductive (0.227) Nervous (0.182) Gastrointestinal (0.159)	Cell proliferation(0.432) Cell proliferation/Cell line (0.205) Inflammation/Trauma(0.228)	pINCY
28	1-2429	Gastrointestinal (1.000)	Cell proliferation(1.000)	pINCY
29	1-50 591-985	Reproductive (0.197) Nervous (0.164) Hematopoietic/Immune (0.145)	Cell proliferation(0.441) Inflammation/Trauma(0.454) Cell proliferation/Cell line (0.191)	pINCY
30	1-285 813-930 1145-3381	Nervous (0.235) Reproductive (0.235) Gastrointestinal (0.126)	Cell proliferation(0.445) Cell proliferation/Cell line (0.202) Inflammation/Trauma(0.252)	pINCY
31	1-82 1728-1803	Reproductive (0.267) Nervous (0.233) Other (0.117)	Cell proliferation(0.383) Inflammation/Trauma(0.383) Cell proliferation/Cell line (0.217)	pINCY
32	1-430 752-964 1405-1515	Reproductive (0.263) Nervous (0.193) Cardiovascular (0.140)	Cell proliferation(0.544) Inflammation/Trauma(0.246) Cell proliferation/Cell line (0.158)	pINCY

Table 3 (Cont.)

Polynucleotide SEQ ID NO:	Fragments	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
33	1-570 860-1573 1859-2494 2864-4416	Nervous (0.383) Reproductive (0.210) Gastrointestinal (0.111)	Cell proliferation(0.395) Inflammation/Trauma(0.334) Cell proliferation/Cell line (0.198)	pINCY
34	1-30 190-234 889-4428	Reproductive (0.280) Nervous (0.195) Hematopoietic/Immune (0.146)	Cell proliferation(0.415) Inflammation/Trauma(0.366) Cell proliferation/Cell line (0.146)	pINCY
35	1-189 264-1907	Reproductive (0.333) Cardiovascular (0.167) Developmental (0.167)	Cell proliferation(0.333) Cell proliferation/Cell line (0.333) Inflammation/Trauma(0.375)	pINCY
36	1-773 1742-1839	Nervous (0.312) Reproductive (0.312) Gastrointestinal (0.125)	Cell proliferation(0.531) Inflammation/Trauma(0.250) Cell proliferation/Cell line (0.125)	pSPORT1
37	1-503	Reproductive (1.000)	Cell proliferation(1.000)	pINCY
38	1-167 449-946 1541-2154	Gastrointestinal (0.723) Reproductive (0.128) Urologic (0.085)	Cell proliferation(0.447) Inflammation/Trauma(0.489) Trauma (0.170)	pINCY
39	1-431 666-733	Reproductive (0.450) Nervous (0.250) Urologic (0.100)	Cell proliferation(0.750) Inflammation/Trauma(0.200) Trauma (0.100)	pINCY
40	1-48 301-453 634-665	Reproductive (0.300) Cardiovascular (0.200) Hematopoietic/Immune (0.200)	Cell proliferation(0.400) Cell proliferation/Cell line (0.300) Inflammation/Trauma(0.400)	pINCY
41	1-276 553-741 820-1235	Hematopoietic/Immune (0.349) Nervous (0.163) Gastrointestinal (0.140)	Inflammation/Trauma(0.512) Cell proliferation(0.349) Cell proliferation/Cell line (0.209)	pINCY

Table 4

Polynucleotide SEQ ID NO:	Library	Library Comment
22	BEPINON01	This normalized bronchial epithelium library was constructed from 5.12 million independent clones from the BEPINOT01 library. RNA was made from a bronchial epithelium primary cell line derived from a 54-year-old Caucasian male. The normalization and hybridization conditions were adapted from Soares et al., PNAS (1994) 91:9228, using a longer (24-hour) reannealing hybridization period.
23	PENITUT01	Library was constructed using RNA isolated from tumor tissue removed from the penis of a 64-year-old Caucasian male during penile amputation. Pathology indicated a fungating invasive grade 4 squamous cell carcinoma involving the inner wall of the foreskin and extending onto the glans penis. Patient history included benign neoplasm of the large bowel, atherosclerotic coronary artery disease, angina pectoris, gout, and obesity. Family history included malignant pharyngeal neoplasm, chronic lymphocytic leukemia, and chronic liver disease.
24	BRAINOT14	Library was constructed using RNA isolated from brain tissue removed from the left frontal lobe of a 40-year-old Caucasian female during excision of a cerebral meningeal lesion. Pathology for the associated tumor tissue indicated grade 4 gemistocytic astrocytoma.
25	BLADNOT05	Library was constructed using RNA isolated from bladder tissue removed from a 60-year-old Caucasian male during a radical cystectomy, prostatectomy, and vasectomy. Pathology for the associated tumor tissue indicated grade 3 transitional cell carcinoma. Carcinoma in-situ was identified in the dome and trigone. Patient history included tobacco use.
26	PROSTUT10	Library was constructed using RNA isolated from prostatic tumor tissue removed from a 66-year-old Caucasian male during radical prostatectomy and regional lymph node excision. Pathology indicated an adenocarcinoma (Gleason grade 2+3). Adenofibromatous hyperplasia was also present. The patient presented with elevated prostate specific antigen (PSA). Family history included prostate cancer and secondary bone cancer.
27	STOMTUT02	Library was constructed using RNA isolated from stomach tumor tissue obtained from a 68-year-old Caucasian female during a partial gastrectomy. Pathology indicated a malignant lymphoma of diffuse large-cell type. Previous surgeries included cholecystectomy. Patient history included thalassemia. Family history included acute leukemia, malignant neoplasm of the esophagus, malignant stomach neoplasm, and atherosclerotic coronary artery disease.

Table 4 (Cont.)

Polynucleotide SEQ ID NO:	Library	Library Comment
28	LSUBNOT03	Library was constructed using RNA isolated from submandibular gland tissue obtained from a 68-year-old Caucasian male during a sialoadenectomy. Family history included acute myocardial infarction, atherosclerotic coronary artery disease, and type II diabetes.
29	BRAINOT09	Library was constructed using RNA isolated from brain tissue removed from a Caucasian male fetus, who died at 23 weeks' gestation.
30	SINTFET03	Library was constructed using RNA isolated from small intestine tissue removed from a Caucasian female fetus, who died at 20 weeks' gestation.
31	TESTTUT02	Library was constructed using RNA isolated from testicular tumor removed from a 31-year-old Caucasian male during unilateral orchiectomy. Pathology indicated embryonal carcinoma.
32	KIDNTUT13	Library was constructed using RNA isolated from kidney tumor tissue removed from a 51-year-old Caucasian female during a nephroureterectomy. Pathology indicated a grade 3 renal cell carcinoma. Patient history included depressive disorder, hypoglycemia, and uterine endometriosis. Family history included calculus of the kidney, colon cancer, and type II diabetes.
33	LUNGTUT07	Library was constructed using RNA isolated from lung tumor tissue removed from the upper lobe of a 50-year-old Caucasian male during segmental lung resection. Pathology indicated an invasive grade 4 squamous cell adenocarcinoma. Patient history included tobacco use. Family history included skin cancer.
34	BRSTNOT13	Library was constructed using RNA isolated from breast tissue removed from the left medial lateral breast of a 36-year-old Caucasian female during bilateral simpl mastectomy and total breast reconstruction. Pathology indicated benign breast tissue. Patient history included a breast neoplasm, depressive disorder, hyperlipidemia, chronic stomach ulcer, and an ectopic pregnancy. Family history included myocardial infarction, cerebrovascular disease, atherosclerotic coronary artery disease, hyperlipidemia, skin cancer, breast cancer, depressive disorder, esophageal cancer, bone cancer, Hodgkin's lymphoma, bladder cancer, and heart condition.
35	CERVNOT03	Library was constructed using RNA isolated from uterine cervical tissue removed from a 40-year-old Caucasian female during a vaginal hysterectomy with bilateral salpingo-oophorectomy and dilation and curettage. Pathology indicated secretory phase endometrium.

Table 4 (Cont.)

Polynucleotide SEQ ID NO:	Library	Library Comment
36	HNT2AZS07	This subtracted library was constructed from RNA isolated from an hNT2 cell line (derived from a human teratocarcinoma that exhibited properties characteristic of a committed neuronal precursor) treated for three days with 0.35 micromolar AZ. The hybridization probe for subtraction was derived from a similarly constructed library from untreated hNT2 cells. 3.08M clones from the AZ-treated library wer subjected to three rounds of subtractive hybridization with 3.04M clones from the untreated library. Subtractive hybridization conditions were based on the methodologies of Swaroop et al. (NAR (1991) 19:1954) and Bonaldo et al. (Genome Research (1996) 6:791).
37	BRSTNOT18	Library was constructed using RNA isolated from diseased breast tissue removed from a 57-year-old Caucasian female during a unilateral simple extended mastectomy. Pathology indicated mildly proliferative breast disease. Patient history included breast cancer and osteoarthritis. Family history included type II diabetes, gallbladder and breast cancer, and chronic lymphocytic leukemia.
38	SYNONOT01	Library was constructed using RNA isolated from synovial tissue removed from a 75-year-old Caucasian male.
39	HEAANOT01	Library was constructed using RNA isolated from right coronary and right circumflex coronary artery tissue removed from the explanted heart of a 46-year-old Caucasian male during a heart transplantation. Patient history included myocardial infarction from total occlusion of the left anterior descending coronary artery, atherosclerotic coronary artery disease, hyperlipidemia, myocardial ischemia. Previous dilated cardiomyopathy, left ventricular dysfunction, and tobacco abuse. Previous surgeries included cardiac catheterization. Family history included atherosclerotic coronary artery disease.
40	BRAINOT21	Library was constructed using RNA isolated from diseased brain tissue removed from the left frontal lobe of a 46-year-old Caucasian male during a lobectomy. Pathology indicated focal cortical and subcortical scarring of the left frontal lobe, characterized by cavitation and extensive reactive changes, including marked gliosis and hemosiderin deposition, consistent with a history of remote severe head trauma. GFAP was positive in astrocytes. The pattern of reactivity is that of reactive gliosis. Patient history included traumatic intracranial hemorrhage and brain injury with loss of consciousness following head trauma. Family history included cerebrovascular disease, cerebrovascular disease, and atherosclerotic coronary artery disease.

Table 4 (Cont.)

Polynucleotide SEQ ID NO:	Library	Library Comment
41	UTRENOT10	Library was constructed using polyA RNA isolated from pooled uterine endometrial tissue removed from three adult females during endometrial biopsy. Pathology indicated normal endometrium.
42		The Incyte cDNAs for SEQ ID NO:42 were derived from cDNA libraries constructed from brain, including tissues associated with Huntington's disease, Alzheimer's disease, and multiple sclerosis, as well as from pituitary, testicular, stomach, spinal cord, kidney, and prostate tissues, and from ovarian, cervical, pancreatic, and soft tissue tumors.

Table 5

Program	Description	Reference	Parameter Threshold
ABI FACTURA	A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
ABI/PARACEL FDF	A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA.	Mismatch <50%
ABI AutoAssembler	A program that assembles nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
BLAST	A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx.	Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410; Altschul, S.F. et al. (1997) Nucleic Acids Res. 25: 3389-3402.	*ESTs*: Probability value= 1.0E-8 or less *Full Length sequences*: Probability value= 1.0E-10 or less
FASTA	A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises as least five functions: fasta, tfasta, fastx, tfastx, and ssearch.	Pearson, W.R. and D.J. Lipman (1988) Proc. Natl. Acad Sci. 85:2444-2448; Pearson, W.R. (1990) Methods Enzymol. 183: 63-98; and Smith, T.F. and M.S. Waterman (1981) Adv. Appl. Math. 2:482-489.	*ESTs*: fasta E value=1.06E-6 *Assembled ESTs*: fasta Identity= 95% or greater and Match length=200 bases or greater; fastx E value=1.0E-8 or less *Full Length sequences*: fastx score=100 or greater
BLIMPS	A BLocks IMProved Searcher that matches a sequence against those in BLOCKS, PRINTS, DOMO, PRODOM, and PFAM databases to search for gene families, sequence homology, and structural fingerprint regions.	Henikoff, S and J.G. Henikoff, Nucl. Acid Res., 19:6565-72, 1991. J.G. Henikoff and S. Henikoff (1996) Methods Enzymol. 266:88-105; and Attwood, T.K. et al. (1997) J. Chem. Inf. Comput. Sci. 37: 417-424.	Score=1000 or greater; Ratio of Score/Strength = 0.75 or larger; and, if applicable, Probability value= 1.0E-3 or less
HMMER	An algorithm for searching a query sequence against hidden Markov model (HMM)-based databases of protein family consensus sequences, such as PFAM.	Krogh, A. et al. (1994) J. Mol. Biol., 235:1501-1531; Sonnhammer, E.L.L. et al. (1988) Nucleic Acids Res. 26:320-322.	Score=10-50 bits for PFAM hits, depending on individual protein families

87

Table 5 (cont.)

Program	Description	Reference	Parameter Threshold
ProfileScan	An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite.	Gribskov, M. et al. (1988) CABIOS 4:61-66; Gribskov, et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25: 217-221.	Normalized quality score≥GCG-specified "HIGH" value for that particular Prosite motif. Generally, score=1.4-2.1.
Phred	A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability.	Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186-194.	
Phrap	A Phils Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences.	Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M. S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA.	Score= 120 or greater; Match length= 56 or greater
Consed	A graphical tool for viewing and editing Phrap assemblies	Gordon, D. et al. (1998) Genome Res. 8:195-202.	
SPScan	A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides.	Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12: 431-439.	Score=3.5 or greater
Motifs	A program that searches amino acid sequences for patterns that matched those defined in Prosite.	Bairoch et al. supra; Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI.	

88

2

What is claimed is:

1. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

5   a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-21,

       b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-21,

       c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-21, and

10   d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-21.

2. An isolated polypeptide of claim 1 selected from the group consisting of SEQ ID NO:1-21.

15

3. An isolated polynucleotide encoding a polypeptide of claim 1.

4. An isolated polynucleotide encoding a polypeptide of claim 2.

20   5. An isolated polynucleotide of claim 4 selected from the group consisting of SEQ ID NO:22-42.

6. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 3.

25

7. A cell transformed with a recombinant polynucleotide of claim 6.

8. A transgenic organism comprising a recombinant polynucleotide of claim 6.

30   9. A method for producing a polypeptide of claim 1, the method comprising:

       a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide encoding the polypeptide of claim 1, and

35   b) recovering the polypeptide so expressed.

10. An isolated antibody which specifically binds to a polypeptide of claim 1.

11. An isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of:

5   a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:22-42,

b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:22-42,

c) a polynucleotide sequence complementary to a),

d) a polynucleotide sequence complementary to b), and

10   e) an RNA equivalent of a)-d).

12. An isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide of claim 11.

15   13. A method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 11, the method comprising:

a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization

20   complex is formed between said probe and said target polynucleotide or fragments thereof, and

b) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.

14. A method of claim 13, wherein the probe comprises at least 60 contiguous nucleotides.

25

15. A method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 11, the method comprising:

a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and

30   b) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

16. A composition comprising an effective amount of a polypeptide of claim 1 and a pharmaceutically acceptable excipient.

35

17. A composition of claim 16, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1-21.

18. A method for treating a disease or condition associated with decreased expression of
5   functional XMAD, comprising administering to a patient in need of such treatment the composition of claim 16.

19. A method for screening a compound for effectiveness as an agonist of a polypeptide of claim 1, the method comprising:
10   a) exposing a sample comprising a polypeptide of claim 1 to a compound, and

b) detecting agonist activity in the sample.

20. A composition comprising an agonist compound identified by a method of claim 19 and a pharmaceutically acceptable excipient.
15

21. A method for treating a disease or condition associated with decreased expression of functional XMAD, comprising administering to a patient in need of such treatment a composition of claim 20.

20   22. A method for screening a compound for effectiveness as an antagonist of a polypeptide of claim 1, the method comprising:

a) exposing a sample comprising a polypeptide of claim 1 to a compound, and

b) detecting antagonist activity in the sample.

25   23. A composition comprising an antagonist compound identified by a method of claim 22 and a pharmaceutically acceptable excipient.

24. A method for treating a disease or condition associated with overexpression of functional XMAD, comprising administering to a patient in need of such treatment a composition of claim 23.
30

25. A method of screening for a compound that specifically binds to the polypeptide of claim 1, said method comprising the steps of:

a) combining the polypeptide of claim 1 with at least one test compound under suitable conditions, and

35   b) detecting binding of the polypeptide of claim 1 to the test compound, thereby identifying a

91

compound that specifically binds to the polypeptide of claim 1.

26. A method of screening for a compound that modulates the activity of the polypeptide of claim 1, said method comprising:

5   a) combining the polypeptide of claim 1 with at least one test compound under conditions permissive for the activity of the polypeptide of claim 1,

b) assessing the activity of the polypeptide of claim 1 in the presence of the test compound, and

c) comparing the activity of the polypeptide of claim 1 in the presence of the test compound

10   with the activity of the polypeptide of claim 1 in the absence of the test compound, wherein a change in the activity of the polypeptide of claim 1 in the presence of the test compound is indicative of a compound that modulates the activity of the polypeptide of claim 1.

27. A method for screening a compound for effectiveness in altering expression of a target

15   polynucleotide, wherein said target polynucleotide comprises a sequence of claim 5, the method comprising:

a) exposing a sample comprising the target polynucleotide to a compound, under conditions suitable for the expression of the target polynucleotide,

b) detecting altered expression of the target polynucleotide, and

20   c) comparing the expression of the target polynucleotide in the presence of varying amounts of the compound and in the absence of the compound.

28. A method for assessing toxicity of a test compound, said method comprising:

a) treating a biological sample containing nucleic acids with the test compound;

25   b) hybridizing the nucleic acids of the treated biological sample with a probe comprising at least 20 contiguous nucleotides of a polynucleotide of claim 11 under conditions whereby a specific hybridization complex is formed between said probe and a target polynucleotide in the biological sample, said target polynucleotide comprising a polynucleotide sequence of a polynucleotide of claim 11 or fragment thereof;

30   c) quantifying the amount of hybridization complex; and

d) comparing the amount of hybridization complex in the treated biological sample with the amount of hybridization complex in an untreated biological sample, wherein a difference in the amount of hybridization complex in the treated biological sample is indicative of toxicity of the test compound.

<110> INCYTE GENOMICS, INC.
    YUE, Henry
    AZIMZAI, Yalda
    TANG, Y. Tom
    PATTERSON, Chandra
    BAUGHN, Mariah R.
    LU, Dyung Aina M.
    SHAH, Purvi
    LAL, Preeti
    AU-YOUNG, Janice
    BURFORD, Neil

<120> EXTRACELLULAR MATRIX AND CELL ADHESION MOLECULES

<130> PF-0760 PCT

<140> To Be Assigned
<141> Herewith

<150> 60/172,852; 60/172,354
<151> 1999-12-10; 1999-12-16

<160> 42
<170> PERL Program

<210> 1
<211> 222
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1424691CD1

<400> 1
Met Arg Gln Ile Ala Ser Asn Thr Ser Leu Gln Arg Ser Gln Ser
 1   5   10   15
Asn Pro Ile Leu Gly Ser Pro Phe Phe Ser His Phe Asp Gly Gln
                20   25   30
Asp Ser Tyr Ala Ala Ala Val Arg Arg Pro Gln Val Pro Ile Lys
                35   40   45
Tyr Gln Gln Ile Thr Pro Val Asn Gln Ser Arg Ser Ser Ser Pro
                50   55   60
Thr Gln Tyr Gly Leu Thr Lys Asn Phe Ser Ser Leu His Leu Asn
                65   70   75
Ser Arg Asp Ser Gly Phe Ser Ser Gly Asn Thr Asp Thr Ser Ser
                80   85   90
Glu Arg Gly Arg Tyr Ser Asp Arg Ser Arg Asn Lys Tyr Gly Arg
                95   100   105
Gly Ser Ile Ser Leu Asn Ser Ser Pro Arg Gly Arg Tyr Ser Gly
                110   115   120
Lys Ser Gln His Ser Thr Pro Ser Arg Gly Arg Tyr Pro Gly Lys
                125   130   135
Phe Tyr Arg Val Ser Gln Ser Ala Leu Asn Pro His Gln Ser Pro
                140   145   150
Asp Phe Lys Arg Ser Pro Arg Asp Leu His Gln Pro Asn Thr Ile
                155   160   165
Pro Gly Met Pro Leu His Pro Glu Thr Asp Ser Arg Ala Ser Glu
                170   175   180
Glu Asp Ser Lys Val Ser Glu Gly Gly Trp Thr Lys Val Glu Tyr
                185   190   195
Arg Lys Lys Pro His Arg Pro Ser Pro Ala Lys Thr Asn Lys Glu
                200   205   210
Arg Ala Arg Gly Asp His Arg Gly Trp Arg Asn Phe
                215   220

<210> 2
<211> 228
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1450801CD1

<400> 2
Met Ile Leu His Asn Gln Ile Thr Gly Ile Gly Arg Glu Asp Phe
1   5   10   15
Ala Thr Thr Tyr Phe Leu Glu Glu Leu Asn Leu Ser Tyr Asn Arg
                20   25   30
Ile Thr Ser Pro Gln Val His Arg Asp Ala Phe Arg Lys Leu Arg
                35   40   45
Leu Leu Arg Ser Leu Asp Leu Ser Gly Asn Arg Leu His Thr Leu
                50   55   60
Pro Pro Gly Leu Pro Arg Asn Val His Val Leu Lys Val Lys Arg
                65   70   75
Asn Glu Leu Ala Ala Leu Ala Arg Gly Ala Leu Ala Gly Met Ala
                80   85   90
Gln Leu Arg Glu Leu Tyr Leu Thr Ser Asn Arg Leu Arg Ser Arg
                95   100   105
Ala Leu Gly Pro Arg Ala Trp Val Asp Leu Ala His Leu Gln Leu
                110   115   120
Leu Asp Ile Ala Gly Asn Gln Leu Thr Glu Ile Pro Glu Gly Leu
                125   130   135
Pro Glu Ser Leu Glu Tyr Leu Tyr Leu Gln Asn Asn Lys Ile Ser
                140   145   150
Ala Val Pro Ala Asn Ala Phe Asp Ser Thr Pro Asn Leu Lys Gly
                155   160   165
Ile Phe Leu Arg Phe Asn Lys Leu Ala Val Gly Ser Val Val Asp
                170   175   180
Ser Ala Phe Arg Arg Leu Lys His Leu Gln Val Leu Asp Ile Glu
                185   190   195
Gly Asn Leu Glu Phe Gly Asp Ile Ser Lys Asp Arg Gly Arg Leu
                200   205   210
Gly Lys Glu Lys Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu
                215   220   225
Glu Thr Arg

<210> 3
<211> 386
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1597872CD1

<400> 3
Met Val His Phe Gln Ala Ser Glu Val Gln Gln Leu Leu His Asn
1   5   10   15
Lys Phe Val Val Ile Leu Gly Asp Ser Ile Gln Arg Ala Val Tyr
                20   25   30
Lys Asp Leu Val Leu Leu Leu Gln Lys Asp Ser Leu Leu Thr Ala
                35   40   45
Ala Gln Leu Lys Ala Lys Tyr Leu Glu Asp Val Leu Glu Glu Leu
                50   55   60
Thr Tyr Gly Pro Ala Pro Asp Leu Val Ile Ile Asn Ser Cys Leu
                65   70   75
Trp Asp Leu Ser Arg Tyr Gly Arg Cys Ser Met Glu Ser Tyr Arg
                80   85   90
Glu Asn Leu Glu Arg Val Phe Val Arg Met Asp Gln Val Leu Pro
                95   100   105

```
Asp Ser Cys Leu Leu Val Trp Asn Met Ala Met Pro Leu Gly Glu
              110                 115                 120
Arg Ile Thr Gly Gly Phe Leu Leu Pro Glu Leu Gln Pro Leu Ala
              125                 130                 135
Gly Ser Leu Arg Arg Asp Val Val Glu Gly Asn Phe Tyr Ser Ala
              140                 145                 150
Thr Leu Ala Gly Asp His Cys Phe Asp Val Leu Asp Leu His Phe
              155                 160                 165
His Phe Arg His Ala Val Gln His Arg His Arg Asp Gly Val His
              170                 175                 180
Trp Asp Gln His Ala His Arg His Leu Ser His Leu Leu Leu Thr
              185                 190                 195
His Val Ala Asp Ala Trp Gly Val Glu Leu Pro Lys Arg Gly Tyr
              200                 205                 210
Pro Pro Asp Pro Trp Ile Glu Asp Trp Ala Glu Met Asn His Pro
              215                 220                 225
Phe Gln Gly Ser His Arg Gln Thr Pro Asp Phe Gly Glu His Leu
              230                 235                 240
Ala Leu Leu Pro Pro Pro Pro Ser Ser Leu Pro Pro Pro Met Pro
              245                 250                 255
Phe Pro Tyr Pro Leu Pro Gln Pro Ser Pro Pro Pro Leu Phe Pro
              260                 265                 270
Pro Leu Pro Gln Asp Thr Pro Phe Phe Pro Gly Gln Pro Phe Pro
              275                 280                 285
Pro His Glu Phe Phe Asn Tyr Asn Pro Val Glu Asp Phe Ser Met
              290                 295                 300
Pro Pro His Leu Gly Cys Gly Pro Gly Val Asn Phe Val Pro Gly
              305                 310                 315
Pro Leu Pro Pro Pro Ile Pro Gly Pro Asn Pro His Gly Gln His
              320                 325                 330
Trp Gly Pro Val Val His Arg Gly Met Pro Arg Tyr Val Pro Asn
              335                 340                 345
Ser Pro Tyr His Val Arg Arg Met Gly Gly Pro Cys Arg Gln Arg
              350                 355                 360
Leu Arg His Ser Glu Arg Leu Ile His Thr Tyr Lys Leu Asp Arg
              365                 370                 375
Arg Pro Pro Ala His Ser Gly Thr Trp Pro Gly
              380                 385
```

```
<210> 4
<211> 833
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1674661CD1

<400> 4
Met Ala Pro His Trp Ala Val Trp Leu Leu Ala Ala Arg Leu Trp
 1               5                  10                  15
Gly Leu Gly Ile Gly Ala Glu Val Trp Trp Asn Leu Val Pro Arg
              20                  25                  30
Lys Thr Val Ser Ser Gly Glu Leu Ala Thr Val Val Arg Arg Phe
              35                  40                  45
Ser Gln Thr Gly Ile Gln Asp Phe Leu Thr Leu Thr Leu Thr Glu
              50                  55                  60
Pro Thr Gly Leu Leu Tyr Val Gly Ala Arg Glu Ala Leu Phe Ala
              65                  70                  75
Phe Ser Met Glu Ala Leu Glu Leu Gln Gly Ala Ile Ser Trp Glu
              80                  85                  90
Ala Pro Val Glu Lys Lys Thr Glu Cys Ile Gln Lys Gly Lys Asn
              95                 100                 105
Asn Gln Thr Glu Cys Phe Asn Phe Ile Arg Phe Leu Gln Pro Tyr
              110                 115                 120
Asn Ala Ser His Leu Tyr Val Cys Gly Thr Tyr Ala Phe Gln Pro
              125                 130                 135
```

```
Lys Cys Thr Tyr Val Asn Met Leu Thr Phe Thr Leu Glu His Gly
            140                 145                 150
Glu Phe Glu Asp Gly Lys Gly Lys Cys Pro Tyr Asp Pro Ala Lys
            155                 160                 165
Gly His Ala Gly Leu Leu Val Asp Gly Glu Leu Tyr Ser Ala Thr
            170                 175                 180
Leu Asn Asn Phe Leu Gly Thr Glu Pro Ile Ile Leu Arg Asn Met
            185                 190                 195
Gly Pro His His Ser Met Lys Thr Glu Tyr Leu Ala Phe Trp Leu
            200                 205                 210
Asn Glu Pro His Phe Val Gly Ser Ala Tyr Val Pro Glu Thr Val
            215                 220                 225
Gly Ser Phe Thr Gly Asp Asp Asp Lys Val Tyr Phe Phe Phe Arg
            230                 235                 240
Glu Arg Ala Leu Glu Ser Asp Cys Tyr Ala Glu Gln Val Val Ala
            245                 250                 255
Arg Val Ala Arg Val Cys Lys Gly Asp Met Gly Gly Ala Arg Thr
            260                 265                 270
Leu Gln Arg Lys Trp Thr Thr Phe Leu Lys Ala Arg Leu Ala Cys
            275                 280                 285
Ser Ala Pro Asn Trp Gln Leu Tyr Phe Asn Gln Leu Gln Ala Met
            290                 295                 300
His Thr Leu Gln Asp Thr Ser Trp His Asn Thr Thr Phe Phe Gly
            305                 310                 315
Val Phe Gln Ala Gln Trp Gly Asp Met Tyr Leu Ser Ala Ile Cys
            320                 325                 330
Glu Tyr Gln Leu Glu Glu Ile Gln Arg Val Phe Glu Gly Pro Tyr
            335                 340                 345
Lys Glu Tyr His Glu Glu Ala Gln Lys Trp Asp Arg Tyr Thr Asp
            350                 355                 360
Pro Val Pro Ser Pro Arg Pro Gly Ser Cys Ile Asn Asn Trp His
            365                 370                 375
Arg Arg His Gly Tyr Thr Ser Ser Leu Glu Leu Pro Asp Asn Ile
            380                 385                 390
Leu Asn Phe Val Lys Lys His Pro Leu Met Glu Glu Gln Val Gly
            395                 400                 405
Pro Arg Trp Ser Arg Pro Leu Leu Val Lys Lys Gly Thr Asn Phe
            410                 415                 420
Thr His Leu Val Ala Asp Arg Val Thr Gly Leu Asp Gly Ala Thr
            425                 430                 435
Tyr Thr Val Leu Phe Ile Gly Thr Gly Asp Gly Trp Leu Leu Lys
            440                 445                 450
Ala Val Ser Leu Gly Pro Trp Val His Leu Ile Glu Glu Leu Gln
            455                 460                 465
Leu Phe Asp Gln Glu Pro Met Arg Ser Leu Val Leu Ser Gln Ser
            470                 475                 480
Lys Lys Leu Leu Phe Ala Gly Ser Arg Ser Gln Leu Val Gln Leu
            485                 490                 495
Pro Val Ala Asp Cys Met Lys Tyr Arg Ser Cys Ala Asp Cys Val
            500                 505                 510
Leu Ala Arg Asp Pro Tyr Cys Ala Trp Ser Val Asn Thr Ser Arg
            515                 520                 525
Cys Val Ala Val Gly Gly His Ser Gly Ser Leu Leu Ile Gln His
            530                 535                 540
Val Met Thr Ser Asp Thr Ser Gly Ile Cys Asn Leu Arg Gly Ser
            545                 550                 555
Lys Lys Val Arg Pro Thr Pro Lys Asn Ile Thr Val Val Ala Gly
            560                 565                 570
Thr Asp Leu Val Leu Pro Cys His Leu Ser Ser Asn Leu Ala His
            575                 580                 585
Ala Arg Trp Thr Phe Gly Gly Arg Asp Leu Pro Ala Glu Gln Pro
            590                 595                 600
Gly Ser Phe Leu Tyr Asp Ala Arg Leu Gln Ala Leu Val Val Met
            605                 610                 615
Ala Ala Gln Pro Arg His Ala Gly Ala Tyr His Cys Phe Ser Glu
            620                 625                 630
Glu Gln Gly Ala Arg Leu Ala Ala Glu Gly Tyr Leu Val Ala Val
```

```
                         635                   640                   645
Val Ala Gly Pro Ser Val Thr Leu Glu Ala Arg Ala Pro Leu Glu
                    650                   655                   660
Asn Leu Gly Leu Val Trp Leu Ala Val Val Ala Leu Gly Ala Val
                    665                   670                   675
Cys Leu Val Leu Leu Leu Leu Val Leu Ser Leu Arg Arg Arg Leu
                    680                   685                   690
Arg Glu Glu Leu Glu Lys Gly Ala Lys Ala Thr Glu Arg Thr Leu
                    695                   700                   705
Val Tyr Pro Leu Glu Leu Pro Lys Glu Pro Thr Ser Pro Pro Phe
                    710                   715                   720
Arg Pro Cys Pro Glu Pro Asp Glu Lys Leu Trp Asp Pro Val Gly
                    725                   730                   735
Tyr Tyr Tyr Ser Asp Gly Ser Leu Lys Ile Val Pro Gly His Ala
                    740                   745                   750
Arg Cys Gln Pro Gly Gly Gly Pro Pro Ser Pro Pro Pro Gly Ile
                    755                   760                   765
Pro Gly Gln Pro Leu Pro Ser Pro Thr Arg Leu His Leu Gly Gly
                    770                   775                   780
Gly Arg Asn Ser Asn Ala Asn Gly Tyr Val Arg Leu Gln Leu Gly
                    785                   790                   795
Gly Glu Asp Arg Gly Gly Leu Gly His Pro Leu Pro Glu Leu Ala
                    800                   805                   810
Asp Glu Leu Arg Arg Lys Leu Gln Gln Arg Gln Pro Leu Pro Asp
                    815                   820                   825
Ser Asn Pro Glu Glu Ser Ser Val
                    830
```

```
<210> 5
<211> 410
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1689337CD1

<400> 5
Met Ser Asn Ile Ser Leu Leu Ala Leu Phe Ser Ser Gln Val Ser
1               5                   10                  15
Ala Ser Leu Lys Ala Leu Ser His Phe Phe Ser Leu Cys Phe Arg
                20                  25                  30
Leu Ala Arg Glu Gln Ala Arg Val Cys Glu Leu Gln Ser Gly Asn
                35                  40                  45
Gln Gln Leu Glu Glu Gln Arg Val Glu Leu Val Glu Arg Leu Gln
                50                  55                  60
Ala Met Leu Gln Ala His Trp Asp Glu Ala Asn Gln Leu Leu Ser
                65                  70                  75
Thr Thr Leu Pro Pro Pro Asn Pro Pro Ala Pro Pro Ala Gly Pro
                80                  85                  90
Ser Ser Pro Gly Pro Gln Glu Pro Glu Lys Glu Glu Arg Arg Val
                95                  100                 105
Trp Thr Met Pro Pro Met Ala Val Ala Leu Lys Pro Val Leu Gln
                110                 115                 120
Gln Ser Arg Glu Ala Arg Asp Glu Leu Pro Gly Ala Pro Pro Val
                125                 130                 135
Leu Cys Ser Ser Ser Ser Asp Leu Ser Leu Leu Leu Gly Pro Ser
                140                 145                 150
Phe Gln Ser Gln His Ser Phe Gln Pro Leu Glu Pro Lys Pro Asp
                155                 160                 165
Leu Thr Ser Ser Thr Ala Gly Ala Phe Ser Ala Leu Gly Ala Phe
                170                 175                 180
His Pro Asp His Arg Ala Glu Arg Pro Phe Pro Glu Glu Asp Pro
                185                 190                 195
Gly Pro Asp Gly Glu Gly Leu Leu Lys Gln Gly Leu Pro Pro Ala
                200                 205                 210
Gln Leu Glu Gly Leu Lys Asn Phe Leu His Gln Leu Leu Glu Thr
```

```
                          215                     220                     225
Val Pro Gln Asn Asn Glu Asn Pro Ser Val Asp Leu Leu Pro Pro
                230                     235                     240
Lys Ser Gly Pro Leu Thr Val Pro Ser Trp Glu Glu Ala Pro Gln
                245                     250                     255
Val Pro Arg Ile Pro Pro Pro Val His Lys Thr Lys Val Pro Leu
                260                     265                     270
Ala Met Ala Ser Ser Leu Phe Arg Val Pro Glu Pro Pro Ser Ser
                275                     280                     285
His Ser Gln Gly Ser Gly Pro Ser Ser Gly Ser Pro Glu Arg Gly
                290                     295                     300
Gly Asp Gly Leu Thr Phe Pro Arg Gln Leu Met Glu Val Ser Gln
                305                     310                     315
Leu Leu Arg Leu Tyr Gln Ala Arg Gly Trp Gly Ala Leu Pro Ala
                320                     325                     330
Glu Asp Leu Leu Leu Tyr Leu Lys Arg Leu Glu His Ser Gly Arg
                335                     340                     345
Thr Asp Gly Arg Gly Asp Asn Val Pro Arg Arg Asn Thr Asp Ser
                350                     355                     360
Arg Leu Gly Glu Ile Pro Arg Lys Glu Ile Pro Ser Gln Ala Val
                365                     370                     375
Pro Arg Arg Leu Ala Thr Ala Pro Lys Thr Glu Lys Pro Pro Ala
                380                     385                     390
Arg Lys Lys Ser Gly His Pro Ala Pro Ser Ser Met Arg Ser Arg
                395                     400                     405
Gly Gly Val Trp Arg
                410


<210> 6
<211> 360
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1746392CD1

<400> 6
Met Asp Thr Pro Leu Arg Arg Ser Arg Arg Leu Gly Gly Leu Arg
  1             5                      10                      15
Pro Glu Ser Pro Glu Ser Leu Thr Ser Val Ser Arg Thr Arg Arg
                20                      25                      30
Ala Leu Val Glu Phe Glu Ser Asn Pro Glu Glu Thr Arg Glu Pro
                35                      40                      45
Gly Ser Pro Pro Ser Val Gln Arg Ala Gly Leu Gly Ser Pro Glu
                50                      55                      60
Arg Pro Pro Lys Thr Ser Pro Gly Ser Pro Arg Leu Gln Gln Gly
                65                      70                      75
Ala Gly Leu Glu Ser Pro Gln Gly Gln Pro Glu Pro Gly Ala Ala
                80                      85                      90
Ser Pro Gln Arg Gln Gln Asp Leu His Leu Glu Ser Pro Gln Arg
                95                      100                     105
Gln Pro Glu Tyr Ser Pro Glu Ser Pro Arg Cys Gln Pro Lys Pro
                110                     115                     120
Ser Glu Glu Ala Pro Lys Cys Ser Gln Asp Gln Gly Val Leu Ala
                125                     130                     135
Ser Glu Leu Ala Gln Asn Lys Glu Glu Leu Thr Pro Gly Ala Pro
                140                     145                     150
Gln His Gln Leu Pro Pro Val Pro Gly Ser Pro Glu Pro Tyr Pro
                155                     160                     165
Gly Gln Gln Ala Pro Gly Pro Glu Pro Ser Gln Pro Leu Leu Glu
                170                     175                     180
Leu Thr Pro Arg Ala Pro Gly Ser Pro Arg Gly Gln His Glu Pro
                185                     190                     195
Ser Lys Pro Pro Pro Ala Gly Glu Thr Val Thr Gly Gly Phe Gly
                200                     205                     210
Ala Lys Lys Arg Lys Gly Ser Ser Ser Gln Ala Pro Ala Ser Lys
```

```
                   215                    220                    225
Lys Leu Asn Lys Glu Glu Leu Pro Val Ile Pro Lys Gly Lys Pro
                   230                    235                    240
Lys Ser Gly Arg Val Trp Lys Asp Arg Ser Lys Lys Arg Phe Ser
                   245                    250                    255
Gln Met Leu Gln Asp Lys Pro Leu Arg Thr Ser Trp Gln Arg Lys
                   260                    265                    270
Met Lys Glu Arg Gln Glu Arg Lys Leu Ala Lys Asp Phe Ala Arg
                   275                    280                    285
His Leu Glu Glu Glu Lys Glu Arg Arg Gln Glu Lys Lys Gln
                   290                    295                    300
Arg Arg Ala Glu Asn Leu Lys Arg Arg Leu Glu Asn Glu Arg Lys
                   305                    310                    315
Ala Glu Val Val Gln Val Ile Arg Asn Pro Ala Lys Leu Lys Arg
                   320                    325                    330
Ala Lys Lys Lys Gln Leu Arg Ser Ile Glu Lys Arg Asp Thr Leu
                   335                    340                    345
Ala Leu Leu Gln Lys Gln Pro Pro Gln Gln Pro Ala Ala Lys Ile
                   350                    355                    360
```

<210> 7
<211> 377
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1825182CD1

<400> 7
```
Met Lys Thr Leu Pro Leu Phe Val Cys Ile Cys Ala Leu Ser Ala
 1               5                    10                    15
Cys Phe Ser Phe Ser Glu Gly Arg Glu Arg Asp His Glu Leu Arg
                   20                    25                    30
His Arg Arg His His His Gln Ser Pro Lys Ser His Phe Glu Leu
                   35                    40                    45
Pro His Tyr Pro Gly Leu Leu Ala His Gln Lys Pro Phe Ile Arg
                   50                  ·  55                    60
Lys Ser Tyr Lys Cys Leu His Lys Arg Cys Arg Pro Lys Leu Pro
                   65                    70                    75
Pro Ser Pro Asn Lys Pro Pro Lys Phe Pro Asn Pro His Gln Pro
                   80                    85                    90
Pro Lys His Pro Asp Lys Asn Ser Ser Val Val Asn Pro Thr Leu
                   95                    100                   105
Val Ala Thr Thr Gln Ile Pro Ser Val Thr Phe Pro Ser Ala Ser
                   110                   115                   120
Thr Lys Ile Thr Thr Leu Pro Asn Val Thr Phe Leu Pro Gln Asn
                   125                   130                   135
Ala Thr Thr Ile Ser Ser Arg Glu Asn Val Asn Thr Ser Ser Ser
                   140                   145                   150
Val Ala Thr Leu Ala Pro Val Asn Ser Pro Ala Pro Gln Asp Thr
                   155                   160                   165
Thr Ala Ala Pro Pro Thr Pro Ser Ala Thr Thr Pro Ala Pro Pro
                   170                   175                   180
Ser Ser Ser Ala Pro Pro Glu Thr Thr Ala Ala Pro Pro Thr Pro
                   185                   190                   195
Ser Ala Thr Thr Gln Ala Pro Pro Ser Ser Ser Ala Pro Pro Glu
                   200                   205                   210
Thr Thr Ala Ala Pro Pro Thr Pro Pro Ala Thr Thr Pro Ala Pro
                   215                   220                   225
Pro Ser Ser Ser Ala Pro Pro Glu Thr Thr Ala Ala Pro Pro Thr
                   230                   235                   240
Pro Ser Ala Thr Thr Pro Ala Pro Leu Ser Ser Ser Ala Pro Pro
                   245                   250                   255
Glu Thr Thr Ala Val Pro Pro Thr Pro Ser Ala Thr Thr Leu Asp
                   260                   265                   270
```

```
Pro Ser Ser Ala Ser Ala Pro Pro Glu Thr Thr Ala Ala Pro Pro
              275                 280                 285
Thr Pro Ser Ala Thr Thr Pro Ala Pro Pro Ser Ser Pro Ala Pro
              290                 295                 300
Gln Glu Thr Thr Ala Ala Pro Ile Thr Thr Pro Asn Ser Ser Pro
              305                 310                 315
Thr Thr Leu Ala Pro Asp Thr Ser Glu Thr Ser Ala Ala Pro Thr
              320                 325                 330
His Gln Thr Thr Thr Ser Val Thr Thr Gln Thr Thr Thr Thr Lys
              335                 340                 345
Gln Pro Thr Ser Ala Pro Gly Gln Asn Lys Ile Ser Arg Phe Leu
              350                 355                 360
Leu Tyr Met Lys Asn Leu Leu Asn Arg Ile Ile Asp Asp Met Val
              365                 370                 375
Glu Gln
```

```
<210> 8
<211> 182
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2155541CD1

<400> 8
Met Leu Val Leu Val Leu Gly Asp Leu His Ile Pro His Arg Cys
1               5                   10                  15
Asn Ser Leu Pro Ala Lys Phe Lys Lys Leu Leu Val Pro Gly Lys
              20                  25                  30
Ile Gln His Ile Leu Cys Thr Gly Asn Leu Cys Thr Lys Glu Ser
              35                  40                  45
Tyr Asp Tyr Leu Lys Thr Leu Ala Gly Asp Val His Ile Val Arg
              50                  55                  60
Gly Asp Phe Asp Glu Asn Leu Asn Tyr Pro Glu Gln Lys Val Val
              65                  70                  75
Thr Val Gly Gln Phe Lys Ile Gly Leu Ile His Gly His Gln Val
              80                  85                  90
Ile Pro Trp Gly Asp Met Ala Ser Leu Ala Leu Leu Gln Arg Gln
              95                  100                 105
Phe Asp Val Asp Ile Leu Ile Ser Gly His Thr His Lys Phe Glu
              110                 115                 120
Ala Phe Glu His Glu Asn Lys Phe Tyr Ile Asn Pro Gly Ser Ala
              125                 130                 135
Thr Gly Ala Tyr Asn Ala Leu Glu Thr Asn Ile Ile Pro Ser Phe
              140                 145                 150
Val Leu Met Asp Ile Gln Ala Ser Thr Val Val Thr Tyr Val Tyr
              155                 160                 165
Gln Leu Ile Gly Asp Asp Val Lys Val Glu Arg Ile Glu Tyr Lys
              170                 175                 180
Lys Pro
```

```
<210> 9
<211> 513
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2215706CD1

<400> 9
Met Asn Met Asn Phe Gly Asp Trp His Leu Phe Arg Ser Thr Val
1               5                   10                  15
Leu Glu Met Arg Asn Ala Glu Ser His Val Val Pro Glu Asp Pro
```

```
                  20                        25                        30
Arg Phe Leu Ser Glu Ser Ser Ser Gly Pro Ala Pro His Gly Glu
                  35                        40                        45
Pro Ala Arg Arg Ala Ser His Asn Glu Leu Pro His Thr Glu Leu
                  50                        55                        60
Ser Ser Gln Thr Pro Tyr Thr Leu Asn Phe Ser Phe Glu Glu Leu
                  65                        70                        75
Asn Thr Leu Gly Leu Asp Glu Gly Ala Pro Arg His Ser Asn Leu
                  80                        85                        90
Ser Trp Gln Ser Gln Thr Arg Arg Thr Pro Ser Leu Ser Ser Leu
                  95                       100                       105
Asn Ser Gln Asp Ser Ser Ile Glu Ile Ser Lys Leu Thr Asp Lys
                 110                       115                       120
Val Gln Ala Glu Tyr Arg Asp Ala Tyr Arg Glu Tyr Ile Ala Gln
                 125                       130                       135
Met Ser Gln Leu Glu Gly Gly Pro Gly Ser Thr Thr Ile Ser Gly
                 140                       145                       150
Arg Ser·Ser Pro His Ser Thr Tyr Tyr Met Gly Gln Ser Ser Ser
                 155                       160                       165
Gly Gly Ser Ile His Ser Asn Leu Glu Gln Glu Lys Gly Lys Asp
                 170                       175                       180
Ser⁻Glu Pro Lys Pro Asp Asp Gly Arg Lys Ser Phe Leu Met Lys
                 185                       190                       195
Arg Gly Asp Val Ile Asp Tyr Ser Ser Ser Gly Val Ser Thr Asn
                 200                       205                       210
Asp Ala Ser Pro Leu Asp Pro Ile Thr Glu Glu Asp Glu Lys Ser
                 215                       220                     · 225
Asp Gln Ser Gly Ser Lys Leu Leu Pro Gly Lys Lys Ser Ser Glu
                 230                       235                       240
Arg Ser Ser Leu Phe Gln Thr Asp Leu Lys Leu Lys Gly Ser Gly
                 245                       250                       255
Leu Arg Tyr Gln Lys Leu Pro Ser Asp Glu Asp Glu Ser Gly Thr
                 260                       265                       270
Glu Glu Ser Asp Asn Thr Pro Leu Leu Lys Asp Asp Lys Asp Arg
                 275                       280                       285
Lys Ala Glu Gly Lys Val Glu Arg Val Pro Lys Ser Pro Glu His
                 290                       295                       300
Ser Ala Glu Pro Ile Arg Thr Phe Ile Lys Ala Lys Glu Tyr Leu
                 305                       310                       315
Ser Asp Ala Leu Leu Asp Lys Lys Asp Ser Ser Asp Ser Gly Val
                 320                       325                       330
Arg Ser Ser Glu Ser Ser Pro Asn His Ser Leu His Asn Glu Val
                 335                       340                       345
Ala Asp Asp Ser His Leu Glu Lys Ala Asn Leu Ile Glu Leu Glu
                 350                       355                       360
Asp Asp Ser His Ser Gly Lys Arg Gly Ile Pro His Ser Leu Ser
                 365                       370                       375
Gly Leu Gln Asp Pro Ile Ile Ala Arg Met Ser Ile Cys Ser Glu
                 380                       385                       390
Asp Lys Lys Ser Pro Ser Glu Cys Ser Leu Ile Ala Ser Ser Pro
                 395                       400                       405
Glu Glu Asn Trp Pro Ala Cys Gln Lys Ala Tyr Asn Leu Asn Arg
                 410                       415                       420
Thr Pro Ser Thr Val Thr Leu Asn Asn Asn Ser Ala Pro Ala Asn
                 425                       430                       435
Arg Ala Asn Gln Asn Phe Asp Glu Met Glu Gly Ile Arg Glu Thr
                 440                       445                       450
Ser Gln Val Ile Leu Arg Pro Ser Ser Ser Pro Asn Pro Thr Thr
                 455                       460                       465
Ile Gln Asn Glu Asn Leu Lys Ser Met Thr His Lys Arg Ser Gln
                 470                       475                       480
Arg Ser Ser Tyr Thr Arg Leu Ser Lys Asp Pro Pro Glu Leu His
                 485                       490                       495
Ala Ala Ala Ser Ser Glu Ser Thr Gly Phe Gly Glu Glu Arg Glu
                 500                       505                       510
Ser Ile Leu
```

```
<210> 10
<211> 361
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2347692CD1

<400> 10
Met Tyr Gly Lys Gly Lys Ser Asn Ser Ser Ala Val Pro Ser Asp
1               5                   10                  15
Ser Gln Ala Arg Glu Lys Leu Ala Leu Tyr Val Tyr Glu Tyr Leu
                20                  25                  30
Leu His Val Gly Ala Gln Lys Ser Ala Gln Thr Phe Leu Ser Glu
                35                  40                  45
Ile Arg Trp Glu Lys Asn Ile Thr Leu Gly Glu Pro Pro Gly Phe
                50                  55                  60
Leu His Ser Trp Trp Cys Val Phe Trp Asp Leu Tyr Cys Ala Ala
                65                  70                  75
Pro Glu Arg Arg Glu Thr Cys Glu His Ser Ser Glu Ala Lys Ala
                80                  85                  90
Phe His Asp Tyr Ser Ala Ala Ala Pro Ser Pro Val Leu Gly
                95                  100                 105
Asn Ile Pro Pro Gly Asp Gly Met Pro Val Gly Pro Val Pro Pro
                110                 115                 120
Gly Phe Phe Gln Pro Phe Met Ser Pro Arg Tyr Pro Gly Gly Pro
                125                 130                 135
Arg Pro Pro Leu Arg Ile Pro Asn Gln Ala Leu Gly Gly Val Pro
                140                 145                 150
Gly Ser Gln Pro Leu Leu Pro Ser Gly Met Asp Pro Thr Arg Gln
                155                 160                 165
Gln Gly His Pro Asn Met Gly Gly Pro Met Gln Arg Met Thr Pro
                170                 175                 180
Pro Arg Gly Met Val Pro Leu Gly Pro Gln Asn Tyr Gly Gly Ala
                185                 190                 195
Met Arg Pro Pro Leu Asn Ala Leu Gly Gly Pro Gly Met Pro Gly
                200                 205                 210
Met Asn Met Gly Pro Gly Gly Gly Arg Pro Trp Pro Asn Pro Thr
                215                 220                 225
Asn Ala Asn Ser Ile Pro Tyr Ser Ser Ala Ser Pro Gly Asn Tyr
                230                 235                 240
Val Gly Pro Pro Gly Gly Gly Gly Pro Pro Gly Thr Pro Ile Met
                245                 250                 255
Pro Ser Pro Ala Asp Ser Thr Asn Ser Gly Asp Asn Met Tyr Thr
                260                 265                 270
Leu Met Asn Ala Val Pro Pro Gly Pro Asn Arg Pro Asn Phe Pro
                275                 280                 285
Met Gly Pro Gly Ser Asp Gly Pro Met Gly Gly Leu Gly Gly Met
                290                 295                 300
Glu Ser His His Met Asn Gly Ser Leu Gly Ser Gly Asp Met Asp
                305                 310                 315
Ser Ile Ser Lys Asn Ser Pro Asn Asn Met Ser Leu Ser Asn Gln
                320                 325                 330
Pro Gly Thr Pro Arg Asp Asp Gly Glu Met Gly Gly Asn Phe Leu
                335                 340                 345
Asn Pro Phe Gln Ser Glu Ser Tyr Ser Pro Ser Met Thr Met Ser
                350                 355                 360
Val


<210> 11
<211> 327
<212> PRT
<213> Homo sapiens

<220>
```

<221> misc_feature
<223> Incyte ID No: 2579048CD1

<400> 11
Met Ala Leu Val His Lys Leu Leu His Gly Thr Tyr Phe Leu Arg
1   5   10   15
Lys Phe Ser Lys Pro Thr Ser Ala Leu Tyr Pro Phe Leu Gly Ile
                20   25   30
Leu Phe Ala Glu Tyr Ser Ser Ser Leu Gln Lys Pro Val Ala Ser
                35   40   45
Pro Gly Lys Ala Ser Ser Gln Arg Lys Thr Glu Gly Asp Leu Gln
                50   55   60
Gly Asp His Gln Lys Glu Val Ala Leu Asp Ile Thr Ser Ser Glu
            65   70   75
Glu Lys Pro Asp Val Ser Phe Asp Lys Ala Ile Arg Asp Glu Ala
                80   85   90
Ile Tyr His Phe Arg Leu Leu Lys Asp Glu Ile Val Asp His Trp
            95   100   105
Arg Gly Pro Glu Gly His Pro Leu His Glu Val Leu Leu Glu Gln
            110   115   120
Ala Lys Val Val Trp Gln Phe Arg Gly Lys Glu Asp Leu Asp Lys
            125   130   135
Trp Thr Val Thr Ser Asp Lys Thr Ile Gly Gly Arg Ser Glu Val
            140   145   150
Phe Leu Lys Met Gly Lys Asn Asn Gln Ser Ala Leu Leu Tyr Gly
                155   160   165
Thr Leu Ser Ser Glu Ala Pro Gln Asp Gly Glu Ser Thr Arg Ser
                170   175   180
Gly Tyr Cys Ala Met Ile Ser Arg Ile Pro Arg Gly Ala Phe Glu
                185   190   195
Arg Lys Met Ser Tyr Asp Trp Ser Gln Phe Asn Thr Leu Tyr Leu
                200   205   210
Arg Val Arg Gly Asp Gly Arg Pro Trp Met Val Asn Ile Lys Glu
            215   220   225
Asp Thr Asp Phe Phe Gln Arg Thr Asn Gln Met Tyr Ser Tyr Phe
                230   235   240
Met Phe Thr Arg Gly Gly Pro Tyr Trp Gln Glu Val Lys Ile Pro
                245   250   255
Phe Ser Lys Phe Phe Phe Ser Asn Arg Gly Arg Ile Arg Asp Val
                260   265   270
Gln His Glu Leu Pro Leu Asp Lys Ile Ser Ser Ile Gly Phe Thr
                275   280   285
Leu Ala Asp Lys Val Asp Gly Pro Phe Phe Leu Glu Ile Asp Phe
                290   295   300
Ile Gly Val Phe Thr Asp Pro Ala His Thr Glu Glu Phe Ala Tyr
                305   310   315
Glu Asn Ser Pro Glu Leu Asn Pro Arg Leu Phe Lys
                320   325

<210> 12
<211> 1110
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2604493CD1

<400> 12
Met Pro Ala Pro Glu Gln Ala Ser Leu Val Glu Glu Gly Gln Pro
1   5   10   15
Gln Thr Arg Gln Glu Ala Ala Ser Thr Gly Pro Gly Met Glu Pro
                20   25   30
Glu Thr Thr Ala Thr Thr Ile Leu Ala Ser Val Lys Glu Gln Glu
                35   40   45
Leu Gln Phe Gln Arg Leu Thr Arg Glu Leu Glu Val Glu Arg Gln
                50   55   60

```
Ile Val Ala Ser Gln Leu Glu Arg Cys Arg Leu Gly Ala Glu Ser
              65                    70                    75
Pro Ser Ile Ala Ser Thr Ser Ser Thr Glu Lys Ser Phe Pro Trp
              80                    85                    90
Arg Ser Thr Asp Val Pro Asn Thr Gly Val Ser Lys Pro Arg Val
              95                   100                   105
Ser Asp Ala Val Gln Pro Asn Asn Tyr Leu Ile Arg Thr Glu Pro
             110                   115                   120
Glu Gln Gly Thr Leu Tyr Ser Pro Glu Gln Thr Ser Leu His Glu
             125                   130                   135
Ser Glu Gly Ser Leu Gly Asn Ser Arg Ser Ser Thr Gln Met Asn
             140                   145                   150
Ser Tyr Ser Asp Ser Gly Tyr Gln Glu Ala Gly Ser Phe His Asn
             155                   160                   165
Ser Gln Asn Val Ser Lys Ala Asp Asn Arg Gln Gln His Ser Phe
             170                   175                   180
Ile Gly Ser Thr Asn Asn His Val Val Arg Asn Ser Arg Ala Glu
             185                   190                   195
Gly Gln Thr Leu Val Gln Pro Ser Val Ala Asn Arg Ala Met Arg
             200                   205                   210
Arg Val Ser Ser Val Pro Ser Arg Ala Gln Ser Pro Ser Tyr Val
             215                   220                   225
Ile Ser Thr Gly Val Ser Pro Ser Arg Gly Ser Leu Arg Thr Ser
             230                   235                   240
Leu Gly Ser Gly Phe Gly Ser Pro Ser Val Thr Asp Pro Arg Pro
             245                   250                   255
Leu Asn Pro Ser Ala Tyr Ser Ser Thr Thr Leu Pro Ala Ala Arg
             260                   265                   270
Ala Ala Ser Pro Tyr Ser Gln Arg Pro Ala Ser Pro Thr Ala Ile
             275                   280                   285
Arg Arg Ile Gly Ser Val Thr Ser Arg Gln Thr Ser Asn Pro Asn
             290                   295                   300
Gly Pro Thr Pro Gln Tyr Gln Thr Thr Ala Arg Val Gly Ser Pro
             305                   310                   315
Leu Thr Leu Thr Asp Ala Gln Thr Arg Val Ala Ser Pro Ser Gln
             320                   325                   330
Gly Gln Val Gly Ser Ser Ser Pro Lys Arg Ser Gly Met Thr Ala
             335                   340                   345
Val Pro Gln His Leu Gly Pro Ser Leu Gln Arg Thr Val His Asp
             350                   355                   360
Met Glu Gln Phe Gly Gln Gln Gln Tyr Asp Ile Tyr Glu Arg Met
             365                   370                   375
Val Pro Pro Arg Pro Asp Ser Leu Thr Gly Leu Arg Ser Ser Tyr
             380                   385                   390
Ala Ser Gln His Ser Gln Leu Gly Gln Asp Leu Arg Ser Ala Val
             395                   400                   405
Ser Pro Asp Leu His Ile Thr Pro Ile Tyr Glu Gly Arg Thr Tyr
             410                   415                   420
Tyr Ser Pro Val Tyr Arg Ser Pro Asn His Gly Thr Val Glu Leu
             425                   430                   435
Gln Gly Ser Gln Thr Ala Leu Tyr Arg Thr Gly Ser Gly Ile Gly
             440                   445                   450
Asn Leu Gln Arg Thr Ser Ser Gln Arg Ser Thr Leu Thr Tyr Gln
             455                   460                   465
Arg Asn Asn Tyr Ala Leu Asn Thr Thr Ala Thr Tyr Ala Glu Pro
             470                   475                   480
Tyr Arg Pro Ile Gln Tyr Arg Val Gln Glu Cys Asn Tyr Asn Arg
             485                   490                   495
Leu Gln His Ala Val Pro Ala Asp Asp Gly Thr Thr Arg Ser Pro
             500                   505                   510
Ser Ile Asp Ser Ile Gln Lys Asp Pro Arg Glu Phe Ala Trp Arg
             515                   520                   525
Asp Pro Glu Leu Pro Glu Val Ile His Met Leu Gln His Gln Phe
             530                   535                   540
Pro Ser Val Gln Ala Asn Ala Ala Ala Tyr Leu Gln His Leu Cys
             545                   550                   555
Phe Gly Asp Asn Lys Val Lys Met Glu Val Cys Arg Leu Gly Gly
```

```
                            560                    565                    570
        Ile Lys His Leu Val Asp Leu Leu Asp His Arg Val Leu Glu Val
                            575                    580                    585
        Gln Lys Asn Ala Cys Gly Ala Leu Arg Asn Leu Val Phe Gly Lys
                            590                    595                    600
        Ser Thr Asp Glu Asn Lys Ile Ala Met Lys Asn Val Gly Gly Ile
                            605                    610                    615
        Pro Ala Leu Leu Arg Leu Leu Arg Lys Ser Ile Asp Ala Glu Val
                            620                    625                    630
        Arg Glu Leu Val Thr Gly Val Leu Trp Asn Leu Ser Ser Cys·Asp
                            635                    640                    645
        Ala Val Lys Met Thr Ile Ile Arg Asp Ala Leu Ser Thr Leu Thr
                            650                    655                    660
        Asn Thr Val Ile Val Pro His Ser Gly Trp Asn Asn Ser Ser Phe
                            665                    670                    675
        Asp Asp Asp His Lys Ile Lys Phe Gln Thr Ser Leu Val Leu Arg
                            680                    685                    690
        Asn Thr Thr Gly Cys Leu Arg Asn Leu Ser Ser Ala Gly Glu Glu
                            695                    700                    705
        Ala Arg Lys Gln Met Arg Ser Cys Glu Gly Leu Val Asp Ser Leu
                            710                    715                    720
        Leu Tyr Val Ile His Thr Cys Val Asn Thr Ser Asp Tyr Asp·Ser
                            725                    730                    735
        Lys Thr Val Glu Asn Cys Val Cys Thr Leu Arg Asn Leu Ser Tyr
                            740                    745                    750
        Arg Leu Glu Leu Glu Val Pro Gln Ala Arg Leu Leu Gly Leu Asn
                            755                    760                    765
        Glu Leu Asp Asp Leu Leu Gly Lys Glu Ser Pro Ser Lys Asp Ser
                            770                    775                    780
        Glu Pro Ser Cys Trp Gly Lys Lys Lys Lys Lys Lys Arg Thr
                            785                    790                    795
        Pro Gln Glu Asp Gln Trp Asp Gly Val Gly Pro Ile Pro Gly Leu
                            800                    805                    810
        Ser Lys Ser Pro Lys Gly Val Glu Met Leu Trp His Pro Ser Val
                            815                    820                    825
        Val Lys Pro Tyr Leu Thr Leu Leu Ala Glu Ser Ser Asn Pro Ala
                            830                    835                    840
        Thr Leu Glu Gly Ser Ala Gly Ser Leu Gln Asn Leu Ser Ala Gly
                            845                    850                    855
        Asn Trp Lys Phe Ala Ala Tyr Ile Arg Ala Ala Val Arg Lys Glu
                            860                    865                    870
        Lys Gly Leu Pro Ile Leu Val Glu Leu Leu Arg Met Asp Asn Asp
                            875                    880                    885
        Arg Val Val Ser Ser Val Ala Thr Ala Leu Arg Asn Met Ala Leu
                            890                    895                    900
        Asp Val Arg Asn Lys Glu Leu Ile Gly Lys Tyr Ala Met Arg Asp
                            905                    910                    915
        Leu Val Asn Arg Leu Pro Gly Gly Asn Gly Pro Ser Val Leu Ser
                            920                    925                    930
        Asp Glu Thr Met Ala Ala Ile Cys Cys Ala Leu His Glu Val Thr
                            935                    940                    945
        Ser Lys Asn Met Glu Asn Ala Lys Ala Leu Ala Asp Ser Gly Gly
                            950                    955                    960
        Ile Glu Lys Leu Val Asn Ile Thr Lys Gly Arg Gly Asp Arg Ser
                            965                    970                    975
        Ser Leu Lys Val Val Lys Ala Ala Ala Gln Val Leu Asn Thr Leu
                            980                    985                    990
        Trp Gln Tyr Arg Asp Leu Arg Ser Ile Tyr Lys Lys Asp Gly Trp
                            995                    1000                   1005
        Asn Gln Asn His Phe Ile Thr Pro Val Ser Thr Leu Glu Arg Asp
                            1010                   1015                   1020
        Arg Phe Lys Ser His Pro Ser Leu Ser Thr Thr Asn Gln Gln Met
                            1025                   1030                   1035
        Ser Pro Ile Ile Gln Ser Val Gly Ser Thr Ser Ser Ser Pro Ala
                            1040                   1045                   1050
        Leu Leu Gly Ile Arg Asp Pro Arg Ser Glu Tyr Asp Arg Thr Gln
                            1055                   1060                   1065
```

```
Pro Pro Met Gln Tyr Tyr Asn Ser Gln Gly Asp Ala Thr His Lys
          1070              1075              1080
Gly Leu Tyr Pro Gly Lys Thr Pro Val Gly Cys Val Ile Gln Ser
          1085              1090              1095
Leu Glu Lys Pro His Phe Gln Ala Leu Gly Gln Trp Pro Gly Lys
          1100              1105              1110
```

<210> 13
<211> 386
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2787182CD1

<400> 13
```
Met Asp Arg Phe Val Trp Thr Ser Gly Leu Leu Glu Ile Asn Glu
  1             5              10              15
Thr Leu Val Ile Gln Gln Arg Gly Val Arg Ile Tyr Asp Gly Glu
             20              25              30
Glu Lys Ile Lys Phe Asp Ala Gly Thr Leu Leu Leu Ser Thr His
             35              40              45
Arg Leu Ile Trp Arg Asp Gln Lys Asn His Glu Cys Cys Met Ala
             50              55              60
Ile Leu Leu Ser Gln Ile Val Phe Ile Glu Glu Gln Ala Ala Gly
             65              70              75
Ile Gly Lys Ser Ala Lys Ile Val Val His Leu His Pro Ala Pro
             80              85              90
Pro Asn Lys Glu Pro Gly Pro Phe Gln Ser Ser Lys Asn Ser Tyr
             95              100             105
Ile Lys Leu Ser Phe Lys Glu His Gly Gln Ile Glu Phe Tyr Arg
             110             115             120
Arg Leu Ser Glu Glu Met Thr Gln Arg Arg Trp Glu Asn Met Pro
             125             130             135
Val Ser Gln Ser Leu Gln Thr Asn Arg Gly Pro Gln Pro Gly Arg
             140             145             150
Ile Arg Ala Val Gly Ile Val Gly Ile Glu Arg Lys Leu Glu Glu
             155             160             165
Lys Lys Lys Glu Thr Asp Lys Asn Ile Ser Glu Ala Phe Glu Asp
             170             175             180
Leu Ser Lys Leu Met Ile Lys Ala Lys Glu Met Val Glu Leu Ser
             185             190             195
Lys Ser Ile Ala Asn Lys Ile Lys Asp Lys Gln Gly Asp Ile Thr
             200             205             210
Glu Asp Glu Thr Ile Arg Phe Lys Ser Tyr Leu Leu Ser Met Gly
             215             220             225
Ile Ala Asn Pro Val Thr Arg Glu Thr Tyr Gly Ser Gly Thr Gln
             230             235             240
Tyr His Met Gln Leu Ala Lys Gln Leu Ala Gly Ile Leu Gln Val
             245             250             255
Pro Leu Glu Glu Arg Gly Gly Ile Met Ser Leu Thr Glu Val Tyr
             260             265             270
Cys Leu Val Asn Arg Ala Arg Gly Met Glu Leu Leu Ser Pro Glu
             275             280             285
Asp Leu Val Asn Ala Cys Lys Met Leu Glu Ala Leu Lys Leu Pro
             290             295             300
Leu Arg Leu Arg Val Phe Asp Ser Gly Val Met Val Ile Glu Leu
             305             310             315
Gln Ser His Lys Glu Glu Glu Met Val Ala Ser Ala Leu Glu Thr
             320             325             330
Val Ser Glu Lys Gly Ser Leu Thr Ser Glu Glu Phe Ala Lys Leu
             335             340             345
Val Gly Met Ser Val Leu Leu Ala Lys Glu Arg Leu Leu Leu Ala
             350             355             360
Glu Lys Met Gly His Leu Cys Arg Asp Asp Ser Val Glu Gly Leu
```

```
                         365                 370                 375
Arg Phe Tyr Pro Asn Leu Phe Met Thr Gln Ser
                         380                 385


<210> 14
<211> 181
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 3096668CD1

<400> 14
Met Glu Val Val Glu Ala Ala Ala Ala Gln Leu Glu Thr Leu Lys
  1               5                  10                  15
Phe Asn Gly Thr Asp Phe Gly Val Gly Glu Gly Pro Ala Ala Pro
                 20                  25                  30
Ser Pro Gly Ser Ala Pro Val Pro Gly Thr Gln Pro Pro Leu Gln
                 35                  40                  45
Ser Phe Glu Gly Ser Pro Asp Ala Gly Gln Thr Val Glu Val Lys
                 50                  55                  60
Pro Ala Gly Glu Gln Pro Leu Gln Pro Val Leu Asn Ala Val Ala
                 65                  70                  75
Ala Gly Thr Pro Ala Pro Gln Pro Gln Pro Pro Ala Glu Ser Pro
                 80                  85                  90
Ala Cys Gly Asp Cys Val Thr Ser Pro Gly Ala Ala Glu Pro Ala
                 95                 100                 105
Arg Ala Pro Asp Ser Leu Glu Thr Ser Asp Ser Asp Ser Asp Ser
                110                 115                 120
Asp Ser Glu Thr Asp Ser Asp Ser Ser Ser Ser Ser Ser Ser Ser
                125                 130                 135
Ser Ser Ser Ser Ser Ser Ser Ser Ser Ser Cys Ile Ser Leu Pro
                140                 145                 150
Pro Val Leu Ser Asp Gly Asp Asp Asp Leu Gln Val Glu Lys Glu
                155                 160                 165
Asn Lys Asn Phe Pro Leu Lys Thr Lys Asp Glu Leu Leu Leu Asn
                170                 175                 180
Leu


<210> 15
<211> 374
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 3143411CD1

<400> 15
Met Arg Pro Gly Thr Ala Leu Gln Ala Val Leu Leu Ala Val Leu
  1               5                  10                  15
Leu Val Gly Leu Arg Ala Ala Thr Gly Arg Leu Leu Ser Gly Gln
                 20                  25                  30
Pro Val Cys Arg Gly Gly Thr Gln Arg Pro Cys Tyr Lys Val Ile
                 35                  40                  45
Tyr Phe His Asp Thr Ser Arg Arg Leu Asn Phe Glu Glu Ala Lys
                 50                  55                  60
Glu Ala Cys Arg Arg Asp Gly Gly Gln Leu Val Ser Ile Glu Ser
                 65                  70                  75
Glu Asp Glu Gln Lys Leu Ile Glu Lys Phe Ile Glu Asn Leu Leu
                 80                  85                  90
Pro Ser Asp Gly Asp Phe Trp Ile Gly Leu Arg Arg Arg Glu Glu
                 95                 100                 105
Lys Gln Ser Asn Ser Thr Ala Cys Gln Asp Leu Tyr Ala Trp Thr
                110                 115                 120
```

```
Asp Gly Ser Ile Ser Gln Phe Arg Asn Trp Tyr Val Asp Glu Pro
              125                 130                 135
Ser Cys Gly Ser Glu Val Cys Val Val Met Tyr His Gln Pro Ser
              140                 145                 150
Ala Pro Ala Gly Ile Gly Gly Pro Tyr Met Phe Gln Trp Asn Asp
              155                 160                 165
Asp Arg Cys Asn Met Lys Asn Asn Phe Ile Cys Lys Tyr Ser Asp
              170                 175                 180
Glu Lys Pro Ala Val Pro Ser Arg Glu Ala Glu Gly Glu Glu Thr
              185                 190                 195
Glu Leu Thr Thr Pro Val Leu Pro Glu Glu Thr Gln Glu Glu Asp
              200                 205                 210
Ala Lys Lys Thr Phe Lys Glu Ser Arg Glu Ala Ala Leu Asn Leu
              215                 220                 225
Ala Tyr Ile Leu Ile Pro Ser Ile Pro Leu Leu Leu Leu Leu Val
              230                 235                 240
Val Thr Thr Val Val Cys Trp Val Trp Ile Cys Arg Lys Arg Lys
              245                 250                 255
Arg Glu Gln Pro Asp Pro Ser Thr Lys Lys Gln His Thr Ile Trp
              260                 265                 270
Pro Ser Pro His Gln Gly Asn Ser Pro Asp Leu Glu Val Tyr Asn
              275                 280                 285
Val Ile Arg Lys Gln Ser Glu Ala Asp Leu Ala Glu Thr Arg Pro
              290                 295                 300
Asp Leu Lys Asn Ile Ser Phe Arg Val Cys Ser Gly Glu Ala Thr
              305                 310                 315
Pro Asp Asp Met Ser Cys Asp Tyr Asp Asn Met Ala Val Asn Pro
              320                 325                 330
Ser Glu Ser Gly Phe Val Thr Leu Val Ser Val Glu Ser Gly Phe
              335                 340                 345
Val Thr Asn Asp Ile Tyr Glu Phe Ser Pro Asp Gln Met Gly Arg
              350                 355                 360
Ser Lys Glu Ser Gly Trp Val Glu Asn Glu Ile Tyr Gly Tyr
              365                 370
```

```
<210> 16
<211> 102
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 3170835CD1

<400> 16
Met Lys Phe Ala Ile Val Leu Phe Ala Leu Phe Ala Val Ala Leu
1               5                   10                  15
Ala Ala Pro Thr Val Glu Val Leu Arg Ser Asp Ser Asn Val Gly
                20                  25                  30
Ile Asp Asn Tyr Ser Tyr Ala Val Glu Thr Ser Asp Gly Thr Ser
                35                  40                  45
Lys Ser Glu Glu Gly Val Leu Lys Asn Ala Gly Thr Glu Leu Glu
                50                  55                  60
Ala Ile Ser Thr His Gly Ser Phe Ser Tyr Val Gly Pro Asp Gly
                65                  70                  75
Gln Thr Tyr Thr Val Thr Tyr Val Ala Asp Glu Asn Gly Phe Gln
                80                  85                  90
Pro Gln Gly Ala His Leu Pro Val Ala Pro Val Ala
                95                  100
```

```
<210> 17
<211> 510
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
```

<223> Incyte ID No: 3550808CD1

<400> 17

```
Met Arg Pro Gly Leu Ser Phe Leu Leu Ala Leu Leu Phe Phe Leu
1                5                  10                 15
Gly Gln Ala Ala Gly Asp Leu Gly Asp Val Gly Pro Pro Ile Pro
                20                 25                 30
Ser Pro Gly Phe Ser Ser Phe Pro Gly Val Asp Ser Ser Ser Ser
                35                 40                 45
Phe Ser Ser Ser Ser Arg Ser Gly Ser Ser Ser Ser Arg Ser Leu
                50                 55                 60
Gly Ser Gly Gly Ser Val Ser Gln Leu Phe Ser Asn Phe Thr Gly
                65                 70                 75
Ser Val Asp Asp Arg Gly Thr Cys Gln Cys Ser Val Ser Leu Pro
                80                 85                 90
Asp Thr Thr Phe Pro Val Asp Arg Val Glu Arg Leu Glu Phe Thr
                95                 100                105
Ala His Val Leu Ser Gln Lys Phe Glu Lys Glu Leu Ser Lys Val
                110                115                120
Arg Glu Tyr Val Gln Leu Ile Ser Val Tyr Glu Lys Lys Leu Leu
                125                130                135
Asn Leu Thr Val Arg Ile Asp Ile Met Glu Lys Asp Thr Ile Ser
                140                145                150
Tyr Thr Glu Leu Asp Phe Glu Leu Ile Lys Val Glu Val Lys Glu
                155                160                165
Met Glu Lys Leu Val Ile Gln Leu Lys Glu Ser Phe Gly Gly Ser
                170                175                180
Ser Glu Ile Val Asp Gln Leu Glu Val Glu Ile Arg Asn Met Thr
                185                190                195
Leu Leu Val Glu Lys Leu Glu Thr Leu Asp Lys Asn Asn Val Leu
                200                205                210
Ala Ile Arg Arg Glu Ile Val Ala Leu Lys Thr Lys Leu Lys Glu
                215                220                225
Cys Glu Ala Ser Lys Asp Gln Asn Thr Pro Val Val His Pro Pro
                230                235                240
Pro Thr Pro Gly Ser Cys Gly His Gly Gly Val Val Asn Ile Ser
                245                250                255
Lys Pro Ser Val Val Gln Leu Asn Trp Arg Gly Phe Ser Tyr Leu
                260                265                270
Tyr Gly Ala Trp Gly Arg Asp Tyr Ser Pro Gln His Pro Asn Lys
                275                280                285
Gly Leu Tyr Trp Val Ala Pro Leu Asn Thr Asp Gly Arg Leu Leu
                290                295                300
Glu Tyr Tyr Arg Leu Tyr Asn Thr Leu Asp Asp Leu Leu Leu Tyr
                305                310                315
Ile Asn Ala Arg Glu Leu Arg Ile Thr Tyr Gly Gln Gly Ser Gly
                320                325                330
Thr Ala Val Tyr Asn Asn Asn Met Tyr Val Asn Met Tyr Asn Thr
                335                340                345
Gly Asn Ile Ala Arg Val Asn Leu Thr Thr Asn Thr Ile Ala Val
                350                355                360
Thr Gln Thr Leu Pro Asn Ala Ala Tyr Asn Asn Arg Phe Ser Tyr
                365                370                375
Ala Asn Val Ala Trp Gln Asp Ile Asp Phe Ala Val Asp Glu Asn
                380                385                390
Gly Leu Trp Val Ile Tyr Ser Thr Glu Ala Ser Thr Gly Asn Met
                395                400                405
Val Ile Ser Lys Leu Asn Asp Thr Thr Leu Gln Val Leu Asn Thr
                410                415                420
Trp Tyr Thr Lys Gln Tyr Lys Pro Ser Ala Ser Asn Ala Phe Met
                425                430                435
Val Cys Gly Val Leu Tyr Ala Thr Arg Thr Met Asn Thr Arg Thr
                440                445                450
Glu Glu Ile Phe Tyr Tyr Tyr Asp Thr Asn Thr Gly Lys Glu Gly
                455                460                465
Lys Leu Asp Ile Val Met His Lys Met Gln Glu Lys Val Gln Ser
                470                475                480
```

```
Ile Asn Tyr Asn Pro Phe Asp Gln Lys Leu Tyr Val Tyr Asn Asp
              485                 490                 495
Gly Tyr Leu Leu Asn Tyr Asp Leu Ser Val Leu Gln Lys Pro Gln
              500                 505                 510


<210> 18
<211> 185
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 3683905CD1

<400> 18
Met Phe Leu Leu Asp Ser Ser Ala Ser Val Ser His Tyr Glu Phe
 1               5                 10                  15
Ser Arg Val Arg Glu Phe Val Gly Gln Leu Val Ala Pro Leu Pro
              20                  25                  30
Leu Gly Thr Gly Ala Leu Arg Ala Ser Leu Val His Val Gly Ser
              35                  40                  45
Arg Pro Tyr Thr Glu Phe Pro Phe Gly Gln His Ser Ser Gly Glu
              50                  55                  60
Ala Ala Gln Asp Ala Val Arg Ala Ser Ala Gln Arg Met Gly Asp
              65                  70                  75
Thr His Thr Gly Leu Ala Leu Val Tyr Ala Lys Glu Gln Leu Phe
              80                  85                  90
Ala Glu Ala Ser Gly Ala Arg Pro Gly Val Pro Lys Val Leu Val
              95                 100                 105
Trp Val Thr Asp Gly Gly Ser Ser Asp Pro Val Gly Pro Pro Met
             110                 115                 120
Gln Glu Leu Lys Asp Leu Gly Val Thr Val Phe Ile Val Ser Thr
             125                 130                 135
Gly Arg Gly Asn Phe Leu Glu Leu Ser Ala Ala Ala Ser Ala Pro
             140                 145                 150
Ala Glu Lys His Leu His Phe Val Asp Val Asp Asp Leu His Ile
             155                 160                 165
Ile Val Gln Glu Leu Arg Gly Ser Ile Leu Asp Ala Met Arg Pro
             170                 175                 180
Gln Ala Tyr Ser Leu
             185

<210> 19
<211> 207
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 4062841CD1

<400> 19
Met Ala Ala Leu Val Glu Pro Leu Gly Leu Glu Arg Asp Val Ser
 1               5                 10                  15
Arg Ala Val Glu Leu Leu Glu Arg Leu Gln Arg Ser Gly Glu Leu
              20                  25                  30
Pro Pro Gln Lys Leu Gln Ala Leu Gln Arg Val Leu Gln Ser Arg
              35                  40                  45
Phe Cys Ser Ala Ile Arg Glu Val Tyr Glu Gln Leu Tyr Asp Thr
              50                  55                  60
Leu Asp Ile Thr Gly Ser Ala Glu Ile Arg Ala His Ala Thr Ala
              65                  70                  75
Lys Ala Thr Val Ala Ala Phe Thr Ala Ser Glu Gly His Ala His
              80                  85                  90
Pro Arg Val Val Glu Leu Pro Lys Thr Asp Glu Gly Leu Gly Phe
              95                 100                 105
```

```
Asn Ile Met Gly Gly Lys Glu Gln Asn Ser Pro Ile Tyr Ile Ser
             110               115               120
Arg Val Ile Pro Gly Gly Val Ala Asp Arg His Gly Gly Leu Lys
             125               130               135
Arg Gly Asp Gln Leu Leu Ser Val Asn Gly Val Ser Val Glu Gly
             140               145               150
Glu Gln His Glu Lys Ala Val Glu Leu Leu Lys Ala Ala Gln Gly
             155               160               165
Ser Val Lys Leu Val Val Arg Tyr Thr Pro Arg Val Leu Glu Glu
             170               175               180
Met Glu Ala Arg Phe Glu Lys Met Arg Ser Ala Arg Arg Arg Gln
             185               190               195
Gln His Gln Ser Tyr Ser Ser Leu Glu Ser Arg Gly
             200               205
```

```
<210> 20
<211> 238
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 6394358CD1

<400> 20
Met Ser Leu Asn Glu His Ser Met Gln Ala Leu Ser Trp Arg Lys
  1           5               10               15
Leu Tyr Leu Ser Arg Ala Lys Leu Lys Ala Ser Ser Arg Thr Ser
             20               25               30
Ala Leu Leu Ser Gly Phe Ala Met Val Ala Met Val Glu Val Gln
             35               40               45
Leu Asp Ala Asp His Asp Tyr Pro Pro Gly Leu Leu Ile Ala Phe
             50               55               60
Ser Ala Cys Thr Thr Val Leu Val Ala Val His Leu Phe Ala Leu
             65               70               75
Met Ile Ser Thr Cys Ile Leu Pro Asn Ile Glu Ala Val Ser Asn
             80               85               90
Val His Asn Leu Asn Ser Val Lys Glu Ser Pro His Glu Arg Met
             95               100              105
His Arg His Ile Glu Leu Ala Trp Ala Phe Ser Thr Val Ile Gly
             110              115              120
Thr Leu Leu Phe Leu Ala Glu Val Val Leu Leu Cys Trp Val Lys
             125              130              135
Phe Leu Pro Leu Lys Lys Gln Pro Gly Gln Pro Arg Pro Thr Ser
             140              145              150
Lys Pro Pro Ala Ser Gly Ala Ala Ala Asn Val Ser Thr Ser Gly
             155              160              165
Ile Thr Pro Gly Gln Ala Ala Ala Ile Ala Ser Thr Thr Ile Met
             170              175              180
Val Pro Phe Gly Leu Ile Phe Ile Val Phe Ala Val His Phe Tyr
             185              190              195
Arg Ser Leu Val Ser His Lys Thr Asp Arg Gln Phe Gln Glu Leu
             200              205              210
Asn Glu Leu Ala Glu Phe Ala Arg Leu Gln Asp Gln Leu Asp His
             215              220              225
Arg Gly Asp His Pro Leu Thr Pro Gly Ser His Tyr Ala
             230              235
```

```
<210> 21
<211> 3298
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2847752CD1
```

<400> 21

```
Met Ala Arg Arg Pro Pro Trp Arg Gly Leu Gly Gly Arg Ser Thr
1               5               10                  15
Pro Ile Leu Leu Leu Leu Leu Leu Ser Leu Phe Pro Leu Ser Gln
                20                  25                  30
Glu Glu Leu Gly Gly Gly Gly His Gln Gly Trp Asp Pro Gly Leu
                35                  40                  45
Ala Ala Thr Thr Gly Pro Arg Ala His Ile Gly Gly Gly Ala Leu
                50                  55                  60
Ala Leu Cys Pro Glu Ser Ser Gly Val Arg Glu Asp Gly Gly Pro
65                  70                  75
Gly Leu Gly Val Arg Glu Pro Ile Phe Val Gly Leu Arg Gly Arg
                80                  85                  90
Arg Gln Ser Ala Arg Asn Ser Arg Gly Pro Pro Glu Gln Pro Asn
                95                  100                 105
Glu Glu Leu Gly Ile Glu His Gly Val Gln Pro Leu Gly Ser Arg
                110                 115                 120
Glu Arg Glu Thr Gly Gln Gly Pro Gly Ser Val Leu Tyr Trp Arg
                125                 130                 135
Pro Glu Val Ser Ser Cys Gly Arg Thr Gly Pro Leu Gln Arg Gly
                140                 145                 150
Ser Leu Ser Pro Gly Ala Leu Ser Ser Gly Val Pro Gly Ser Gly
                155                 160                 165
Asn Ser Ser Pro Leu Pro Ser Asp Phe Leu Ile Arg His His Gly
                170                 175                 180
Pro Lys Pro Val Ser Ser Gln Arg Asn Ala Gly Thr Gly Ser Arg
                185                 190                 195
Lys Arg Val Gly Thr Ala Arg Cys Cys Gly Glu Leu Trp Ala Thr
                200                 205                 210
Gly Ser Lys Gly Gln Gly Glu Arg Ala Thr Thr Ser Gly Ala Glu
                215                 220                 225
Arg Thr Ala Pro Arg Arg Asn Cys Leu Pro Gly Ala Ser Gly Ser
                230                 235                 240
Gly Pro Glu Leu Asp Ser Ala Pro Arg Thr Ala Arg Thr Ala Pro
                245                 250                 255
Ala Ser Gly Ser Ala Pro Arg Glu Ser Arg Thr Ala Pro Glu Pro
                260                 265                 270
Ala Pro Lys Arg Met Arg Ser Arg Gly Leu Phe Arg Cys Arg Phe
                275                 280                 285
Leu Pro Gln Arg Pro Gly Pro Arg Pro Pro Gly Leu Pro Ala Arg
                290                 295                 300
Pro Glu Ala Arg Lys Val Thr Ser Ala Asn Arg Ala Arg Phe Arg
                305                 310                 315
Arg Ala Ala Asn Arg His Pro Gln Phe Pro Gln Tyr Asn Tyr Gln
                320                 325                 330
Thr Leu Val Pro Glu Asn Glu Ala Ala Gly Thr Ala Val Leu Arg
                335                 340                 345
Val Val Ala Gln Asp Pro Asp Ala Gly Glu Ala Gly Arg Leu Val
                350                 355                 360
Tyr Ser Leu Ala Ala Leu Met Asn Ser Arg Ser Leu Glu Leu Phe
                365                 370                 375
Ser Ile Asp Pro Gln Ser Gly Leu Ile Arg Thr Ala Ala Ala Leu
                380                 385                 390
Asp Arg Glu Ser Met Glu Arg His Tyr Leu Arg Val Thr Ala Gln
                395                 400                 405
Asp His Gly Ser Pro Arg Leu Ser Ala Thr Thr Met Val Ala Val
                410                 415                 420
Thr Val Ala Asp Arg Asn Asp His Ser Pro Val Phe Glu Gln Ala
                425                 430                 435
Gln Tyr Arg Glu Thr Leu Arg Glu Asn Val Glu Glu Gly Tyr Pro
                440                 445                 450
Ile Leu Gln Leu Arg Ala Thr Asp Gly Asp Ala Pro Pro Asn Ala
                455                 460                 465
Asn Leu Arg Tyr Arg Phe Val Gly Pro Pro Ala Ala Arg Ala Ala
                470                 475                 480
Ala Ala Ala Ala Phe Glu Ile Asp Pro Arg Ser Gly Leu Ile Ser
                485                 490                 495
```

20/42

Thr Ser Gly Arg Val Asp Arg Glu His Met Glu Ser Tyr Glu Leu
                500   505   510
Val Val Glu Ala Ser Asp Gln Gly Gln Glu Pro Gly Pro Arg Ser
                515   520   525
Ala Thr Val Arg Val His Ile Thr Val Leu Asp Glu Asn Asp Asn
                530   535   540
Ala Pro Gln Phe Ser Glu Lys Arg Tyr Val Ala Gln Val Arg Glu
                545   550   555
Asp Val Arg Pro His Thr Val Val Leu Arg Val Thr Ala Thr Asp
                560   565   570
Arg Asp Lys Asp Ala Asn Gly Leu Val His Tyr Asn Ile Ile Ser
                575   580   585
Gly Asn Ser Arg Gly His Phe Ala Ile Asp Ser Leu Thr Gly Glu
                590   595   600
Ile Gln Val Val Ala Pro Leu Asp Phe Glu Ala Glu Arg Glu Tyr
                605   610   615
Ala Leu Arg Ile Arg Ala Gln Asp Ala Gly Arg Pro Pro Leu Ser
                620   625   630
Asn Asn Thr Gly Leu Ala Ser Ile Gln Val Asp Ile Asn Asp
                635   640   645
His Ile Pro Ile Phe Val Ser Thr Pro Phe Gln Val Ser Val Leu
                650   655   660
Glu Asn Ala Pro Leu Gly His Ser Val Ile His Ile Gln Ala Val
                665   670   675
Asp Ala Asp His Gly Glu Asn Ala Arg Leu Glu Tyr Ser Leu Thr
                680   685   690
Gly Val Ala Pro Asp Thr Pro Phe Val Ile Asn Ser Ala Thr Gly
                695   700   705
Trp Val Ser Val Ser Gly Pro Leu Asp Arg Glu Ser Val Glu His
                710   715   720
Tyr Phe Phe Gly Val Glu Ala Arg Asp His Gly Ser Pro Pro Leu
                725   730   735
Ser Ala Ser Ala Ser Val Thr Val Thr Val Leu Asp Val Asn Asp
                740   745   750
Asn Arg Pro Glu Phe Thr Met Lys Glu Tyr His Leu Arg Leu Asn
                755   760   765
Glu Asp Ala Ala Val Gly Thr Ser Val Val Ser Val Thr Ala Val
                770   775   780
Asp Arg Asp Ala Asn Ser Ala Ile Ser Tyr Gln Ile Thr Gly Gly
                785   790   795
Asn Thr Arg Asn Arg Phe Ala Ile Ser Thr Gln Gly Gly Val Gly
                800   805   810
Leu Val Thr Leu Ala Leu Pro Leu Asp Tyr Lys Gln Glu Arg Tyr
                815   820   825
Phe Lys Leu Val Leu Thr Ala Ser Asp Arg Ala Leu His Asp His
                830   835   840
Cys Tyr Val His Ile Asn Ile Thr Asp Ala Asn Thr His Arg Pro
                845   850   855
Val Phe Gln Ser Ala His Tyr Ser Val Ser Val Asn Glu Asp Arg
                860   865   870
Pro Met Gly Ser Thr Ile Val Val Ile Ser Ala Ser Asp Asp Asp
                875   880   885
Val Gly Glu Asn Ala Arg Ile Thr Tyr Leu Leu Glu Asp Asn Leu
                890   895   900
Pro Gln Phe Arg Ile Asp Ala Asp Ser Gly Ala Ile Thr Leu Gln
                905   910   915
Ala Pro Leu Asp Tyr Glu Asp Gln Val Thr Tyr Thr Leu Ala Ile
                920   925   930
Thr Ala Arg Asp Asn Gly Ile Pro Gln Lys Ala Asp Thr Thr Tyr
                935   940   945
Val Glu Val Met Val Asn Asp Val Asn Asp Asn Ala Pro Gln Phe
                950   955   960
Val Ala Ser His Tyr Thr Gly Leu Val Ser Glu Asp Ala Pro Pro
                965   970   975
Phe Thr Ser Val Leu Gln Ile Ser Ala Thr Asp Arg Asp Ala His
                980   985   990
Ala Asn Gly Arg Val Gln Tyr Thr Phe Gln Asn Gly Glu Asp Gly

21/42

```
                    995                 1000                1005
Asp Gly Asp Phe Thr Ile Glu Pro Thr Ser Gly Ile Val Arg Thr
                   1010                1015                1020
Val Arg Arg Leu Asp Arg Glu Ala Val Ser Val Tyr Glu Leu Thr
                   1025                1030                1035
Ala Tyr Ala Val Asp Arg Gly Val Pro Pro Leu Arg Thr Pro Val
                   1040                1045                1050
Ser Ile Gln Val Met Val Gln Asp Val Asn Asp Asn Ala Pro Val
                   1055                1060                1065
Phe Pro Ala Glu Glu Phe Glu Val Arg Val Lys Glu Asn Ser Ile
                   1070                1075                1080
Val Gly Ser Val Val Ala Gln Ile Thr Ala Val Asp Pro Asp Glu
                   1085                1090                1095
Gly Pro Asn Ala His Ile Met Tyr Gln Ile Val Glu Gly Asn Ile
                   1100                1105                1110
Pro Glu Leu Phe Gln Met Asp Ile Phe Ser Gly Glu Leu Thr Ala
                   1115                1120                1125
Leu Ile Asp Leu Asp Tyr Glu Ala Arg Gln Glu Tyr Val Ile Val
                   1130                1135                1140
Val Gln Ala Thr Ser Ala Pro Leu Val Ser Arg Ala Thr Val His
                   1145                1150                1155
Val Arg Leu Val Asp Gln Asn Asp Asn Ser Pro Val Leu Asn Asn
                   1160                1165                1170
Phe Gln Ile Leu Phe Asn Asn Tyr Val Ser Asn Arg Ser Asp Thr
                   1175                1180                1185
Phe Pro Ser Gly Ile Ile Gly Arg Ile Pro Ala Tyr Asp Pro Asp
                   1190                1195                1200
Val Ser Asp His Leu Phe Tyr Ser Phe Glu Arg Gly Asn Glu Leu
                   1205                1210                1215
Gln Leu Leu Val Val Asn Gln Thr Ser Gly Glu Leu Arg Leu Ser
                   1220                1225                1230
Arg Lys Leu Asp Asn Asn Arg Pro Leu Val Ala Ser Met Leu Val
                   1235                1240                1245
Thr Val Thr Asp Gly Leu His Ser Val Thr Ala Gln Cys Val Leu
                   1250                1255                1260
Arg Val Val Ile Ile Thr Glu Glu Leu Leu Ala Asn Ser Leu Thr
                   1265                1270                1275
Val Arg Leu Glu Asn Met Trp Gln Glu Arg Phe Leu Ser Pro Leu
                   1280                1285                1290
Leu Gly Arg Phe Leu Glu Gly Val Ala Ala Val Leu Ala Thr Pro
                   1295                1300                1305
Ala Glu Asp Val Phe Ile Phe Asn Ile Gln Asn Asp Thr Asp Val
                   1310                1315                1320
Gly Gly Thr Val Leu Asn Val Ser Phe Ser Ala Leu Ala Pro Arg
                   1325                1330                1335
Gly Ala Gly Ala Gly Ala Ala Gly Pro Trp Phe Ser Ser Glu Glu
                   1340                1345                1350
Leu Gln Glu Gln Leu Tyr Val Arg Arg Ala Ala Leu Ala Ala Arg
                   1355                1360                1365
Ser Leu Leu Asp Val Leu Pro Phe Asp Asp Asn Val Cys Leu Arg
                   1370                1375                1380
Glu Pro Cys Glu Asn Tyr Met Lys Cys Val Ser Val Leu Arg Phe
                   1385                1390                1395
Asp Ser Ser Ala Pro Phe Leu Ala Ser Ala Ser Thr Leu Phe Arg
                   1400                1405                1410
Pro Ile Gln Pro Ile Ala Gly Leu Arg Cys Arg Cys Pro Pro Gly
                   1415                1420                1425
Phe Thr Gly Asp Phe Cys Glu Thr Glu Leu Asp Leu Cys Tyr Ser
                   1430                1435                1440
Asn Pro Cys Arg Asn Gly Gly Ala Cys Ala Arg Arg Glu Gly Gly
                   1445                1450                1455
Tyr Thr Cys Val Cys Arg Pro Arg Phe Thr Gly Glu Asp Cys Glu
                   1460                1465                1470
Leu Asp Thr Glu Ala Gly Arg Cys Val Pro Gly Val Cys Arg Asn
                   1475                1480                1485
Gly Gly Thr Cys Thr Asp Ala Pro Asn Gly Gly Phe Arg Cys Gln
                   1490                1495                1500
```

22/42

Cys Pro Ala Gly Gly Ala Phe Glu Gly Pro Arg Cys Glu Val Ala
          1505   1510   1515
Ala Arg Ser Phe Pro Pro Ser Ser Phe Val Met Phe Arg Gly Leu
          1520   1525   1530
Arg Gln Arg Phe His Leu Thr Leu Ser Leu Ser Phe Ala Thr Val
          1535   1540   1545
Gln Gln Ser Gly Leu Leu Phe Tyr Asn Gly Arg Leu Asn Glu Lys
          1550   1555   1560
His Asp Phe Leu Ala Leu Glu Leu Val Ala Gly Gln Val Arg Leu
          1565   1570   1575
Thr Tyr Ser Thr Gly Glu Ser Asn Thr Val Val Ser Pro Thr Val
          1580   1585   1590
Pro Gly Gly Leu Ser Asp Gly Gln Trp His Thr Val His Leu Arg
          1595   1600   1605
Tyr Tyr Asn Lys Pro Arg Thr Asp Ala Leu Gly Gly Ala Gln Gly
          1610   1615   1620
Pro Ser Lys Asp Lys Val Ala Val Leu Ser Val Asp Asp Cys Asp
          1625   1630   1635
Val Ala Val Ala Leu Gln Phe Gly Ala Glu Ile Gly Asn Tyr Ser
          1640   1645   1650
Cys Ala Ala Ala Gly Val Gln Thr Ser Ser Lys Lys Ser Leu Asp
          1655   1660   1665
Leu Thr Gly Pro Leu Leu Leu Gly Gly Val Pro Asn Leu Pro Glu
          1670   1675   1680
Asn Phe Pro Val Ser His Lys Asp Phe Ile Gly Cys Met Arg Asp
          1685   1690   1695
Leu His Ile Asp Gly Arg Arg Val Asp Met Ala Ala Phe Val Ala
          1700   1705   1710
Asn Asn Gly Thr Met Ala Gly Cys Gln Ala Lys Leu His Phe Cys
          1715   1720   1725
Asp Ser Gly Pro Cys Lys Asn Ser Gly Phe Cys Ser Glu Arg Trp
          1730   1735   1740
Gly Ser Phe Ser Cys Asp Cys Pro Val Gly Phe Gly Gly Lys Asp
          1745   1750   1755
Cys Gln Leu Thr Met Ala His Pro His His Phe Arg Gly Asn Gly
          1760   1765   1770
Thr Leu Ser Trp Asn Phe Gly Ser Asp Met Ala Val Ser Val Pro
          1775   1780   1785
Trp Tyr Leu Gly Leu Ala Phe Arg Thr Arg Ala Thr Gln Gly Val
          1790   1795   1800
Leu Met Gln Val Gln Ala Gly Pro His Ser Thr Leu Leu Cys Gln
          1805   1810   1815
Leu Asp Arg Gly Leu Leu Ser Val Thr Val Thr Arg Gly Ser Gly
          1820   1825   1830
Arg Ala Ser His Leu Leu Leu Asp Gln Val Thr Val Ser Asp Gly
          1835   1840   1845
Arg Trp His Asp Leu Arg Leu Glu Leu Gln Glu Glu Pro Gly Gly
          1850   1855   1860
Arg Arg Gly His His Val Leu Met Val Ser Leu Asp Phe Ser Leu
          1865   1870   1875
Phe Gln Asp Thr Met Ala Val Gly Ser Glu Leu Gln Gly Leu Lys
          1880   1885   1890
Val Lys Gln Leu His Val Gly Gly Leu Pro Pro Gly Ser Ala Glu
          1895   1900   1905
Glu Ala Pro Gln Gly Leu Val Gly Cys Ile Gln Pro Pro Ser Glu
          1910   1915   1920
Cys Gly Pro Gly Cys Val Val Thr Asn Ala Cys Ala Ser Gly Pro
          1925   1930   1935
Cys Pro Pro His Ala Asp Cys Arg Asp Leu Trp Gln Thr Phe Ser
          1940   1945   1950
Cys Thr Cys Gln Pro Gly Tyr Tyr Gly Pro Gly Cys Val Asp Ala
          1955   1960   1965
Cys Leu Leu Asn Pro Cys Gln Asn Gln Gly Ser Cys Arg His Leu
          1970   1975   1980
Pro Gly Ala Pro His Gly Tyr Thr Cys Asp Cys Val Gly Gly Tyr
          1985   1990   1995
Phe Gly His His Cys Glu His Arg Met Asp Gln Gln Cys Pro Arg

```
              2000              2005             2010
Gly Trp Trp Gly Ser Pro Thr Cys Gly Pro Cys Asn Cys Asp Val
              2015              2020             2025
His Lys Gly Phe Asp Pro Asn Cys Asn Lys Thr Asn Gly Gln Cys
              2030              2035             2040
His Cys Lys Glu Phe His Tyr Arg Pro Arg Gly Ser Asp Ser Cys
              2045              2050             2055
Leu Pro Cys Asp Cys Tyr Pro Val Gly Ser Thr Ser Arg Ser Cys
              2060              2065             2070
Ala Pro His Ser Gly Gln Cys Pro Cys Arg Pro Gly Ala Leu Gly
              2075              2080             2085
Arg Gln Cys Asn Ser Cys Asp Ser Pro Phe Ala Glu Val Thr Ala
              2090              2095             2100
Ser Gly Cys Arg Val Leu Tyr Asp Ala Cys Pro Lys Ser Leu Arg
              2105              2110             2115
Ser Gly Val Trp Trp Pro Gln Thr Lys Phe Gly Val Leu Ala Thr
              2120              2125             2130
Val Pro Cys Pro Arg Gly Ala Leu Gly Leu Arg Gly Ala Gly Ala
              2135              2140             2145
Ala Val Arg Leu Cys Asp Glu Ala Gln Gly Trp Leu Glu Pro Asp
              2150              2155             2160
Leu Phe Asn Cys Thr Ser Pro Ala Phe Arg Glu Leu Ser Leu Leu
              2165              2170             2175
Leu Asp Gly Leu Glu Leu Asn Lys Thr Ala Leu Asp Thr Met Glu
              2180              2185             2190
Ala Lys Lys Leu Ala Gln Arg Leu Arg Glu Val Thr Gly His Thr
              2195              2200             2205
Asp His Tyr Phe Ser Gln Asp Val Arg Val Thr Ala Arg Leu Leu
              2210              2215             2220
Ala His Leu Leu Ala Phe Glu Ser His Gln Gln Gly Phe Gly Leu
              2225              2230             2235
Thr Ala Thr Gln Asp Ala His Phe Asn Glu Asn Leu Leu Trp Ala
              2240              2245             2250
Gly Ser Ala Leu Leu Ala Pro Glu Thr Gly Asp Leu Trp Ala Ala
              2255              2260             2265
Leu Gly Gln Arg Ala Pro Gly Gly Ser Pro Gly Ser Ala Gly Leu
              2270              2275             2280
Val Arg His Leu Glu Glu Tyr Ala Ala Thr Leu Ala Arg Asn Met
              2285              2290             2295
Glu Leu Thr Tyr Leu Asn Pro Met Gly Leu Val Thr Pro Asn Ile
              2300              2305             2310
Met Leu Ser Ile Asp Arg Met Glu His Pro Ser Ser Pro Arg Gly
              2315              2320             2325
Ala Arg Arg Tyr Pro Arg Tyr His Ser Asn Leu Phe Arg Gly Gln
              2330              2335             2340
Asp Ala Trp Asp Pro His Thr His Val Leu Leu Pro Ser Gln Ser
              2345              2350             2355
Pro Arg Pro Ser Pro Ser Glu Val Leu Pro Thr Ser Ser Ser Ile
              2360              2365             2370
Glu Asn Ser Thr Thr Ser Ser Val Val Pro Pro Pro Ala Pro Pro
              2375              2380             2385
Glu Pro Glu Pro Gly Ile Ser Ile Ile Ile Leu Leu Val Tyr Arg
              2390              2395             2400
Thr Leu Gly Gly Leu Leu Pro Ala Gln Phe Gln Ala Glu Arg Arg
              2405              2410             2415
Gly Ala Arg Leu Pro Gln Asn Pro Val Met Asn Ser Pro Val Val
              2420              2425             2430
Ser Val Ala Val Phe His Gly Arg Asn Phe Leu Arg Gly Ile Leu
              2435              2440             2445
Glu Ser Pro Ile Ser Leu Glu Phe Arg Leu Leu Gln Thr Ala Asn
              2450              2455             2460
Arg Ser Lys Ala Ile Cys Val Gln Trp Asp Pro Pro Gly Leu Ala
              2465              2470             2475
Glu Gln His Gly Val Trp Thr Ala Arg Asp Cys Glu Leu Val His
              2480              2485             2490
Arg Asn Gly Ser His Ala Arg Cys Arg Cys Ser Arg Thr Gly Thr
              2495              2500             2505
```

Phe Gly Val Leu Met Asp Ala Ser Pro Arg Glu Arg Leu Glu Gly
          2510   2515   2520
Asp Leu Glu Leu Leu Ala Val Phe Thr His Val Val Val Ala Val
          2525   2530   2535
Ser Val Ala Ala Leu Val Leu Thr Ala Ala Ile Leu Leu Ser Leu
          2540   2545   2550
Arg Ser Leu Lys Ser Asn Val Arg Gly Ile His Ala Asn Val Ala
          2555   2560   2565
Ala Ala Leu Gly Val Ala Glu Leu Leu Phe Leu Leu Gly Ile His
          2570   2575   2580
Arg Thr His Asn Gln Leu Val Cys Thr Ala Val Ala Ile Leu Leu
          2585   2590   2595
His Tyr Phe Phe Leu Ser Thr Phe Ala Trp Leu Phe Val Gln Gly
          2600   2605   2610
Leu His Leu Tyr Arg Met Gln Val Glu Pro Arg Asn Val Asp Arg
          2615   2620   2625
Gly Ala Met Arg Phe Tyr His Ala Leu Gly Trp Gly Val Pro Ala
          2630   2635   2640
Val Leu Leu Gly Leu Ala Val Gly Leu Asp Pro Glu Gly Tyr Gly
          2645   2650   2655
Asn Pro Asp Phe Cys Trp Ile Ser Val His Glu Pro Leu Ile Trp
          2660   2665   2670
Ser Phe Ala Gly Pro Val Val Leu Val Ile Val Met Asn Gly Thr
          2675   2680   2685
Met Phe Leu Leu Ala Ala Arg Thr Ser Cys Ser Thr Gly Gln Arg
          2690   2695   2700
Glu Ala Lys Lys Thr Ser Ala Leu Thr Leu Arg Ser Ser Phe Leu
          2705   2710   2715
Leu Leu Leu Leu Val Ser Ala Ser Trp Leu Phe Gly Leu Leu Ala
          2720   2725   2730
Val Asn His Ser Ile Leu Ala Phe His Tyr Leu His Ala Gly Leu
          2735   2740   2745
Cys Gly Leu Gln Gly Leu Ala Val Leu Leu Leu Phe Cys Val Leu
          2750   2755   2760
Asn Ala Asp Ala Arg Ala Ala Trp Met Pro Ala Cys Leu Gly Arg
          2765   2770   2775
Lys Ala Ala Pro Glu Glu Ala Arg Pro Ala Pro Gly Leu Gly Pro
          2780   2785   2790
Gly Ala Tyr Asn Asn Thr Ala Leu Phe Glu Glu Ser Gly Leu Ile
          2795   2800   2805
Arg Ile Thr Leu Gly Ala Ser Thr Val Ser Ser Val Ser Ser Ala
          2810   2815   2820
Arg Ser Gly Arg Thr Gln Asp Gln Asp Ser Gln Arg Gly Arg Ser
          2825   2830   2835
Tyr Leu Arg Asp Asn Val Leu Val Arg His Gly Ser Ala Ala Asp
          2840   2845   2850
His Thr Asp His Ser Leu Gln Ala His Ala Gly Pro Thr Asp Leu
          2855   2860   2865
Asp Val Ala Met Phe His Arg Asp Ala Gly Ala Asp Ser Asp Ser
          2870   2875   2880
Asp Ser Asp Leu Ser Leu Glu Glu Glu Arg Ser Leu Ser Ile Pro
          2885   2890   2895
Ser Ser Glu Ser Glu Asp Asn Gly Arg Thr Arg Gly Arg Val Gln
          2900   2905   2910
Arg Pro Leu Cys Arg Ala Ala Gln Ser Glu Arg Leu Leu Thr His
          2915   2920   2925
Pro Lys Asp Val Asp Gly Asn Asp Leu Leu Ser Tyr Trp Pro Ala
          2930   2935   2940
Leu Gly Glu Cys Glu Ala Ala Pro Cys Ala Leu Gln Thr Trp Gly
          2945   2950   2955
Ser Glu Arg Arg Leu Gly Leu Asp Thr Ser Lys Asp Ala Ala Asn
          2960   2965   2970
Asn Asn Gln Pro Asp Pro Ala Leu Thr Ser Gly Asp Glu Thr Ser
          2975   2980   2985
Leu Gly Arg Ala Gln Arg Gln Arg Lys Gly Ile Leu Lys Asn Arg
          2990   2995   3000
Leu Gln Tyr Pro Leu Val Pro Gln Thr Arg Gly Ala Pro Glu Leu

```
               3005                   3010                   3015
Ser Trp Cys Arg Ala Ala Thr Leu Gly His Arg Ala Val Pro Ala
               3020                   3025                   3030
Ala Ser Tyr Gly Arg Ile Tyr Ala Gly Gly Gly Thr Gly Ser Leu
               3035                   3040                   3045
Ser Gln Pro Ala Ser Arg Tyr Ser Ser Arg Glu Gln Leu Asp Leu
               3050                   3055                   3060
Leu Leu Arg Arg Gln Leu Ser Arg Glu Arg Leu Glu Glu Ala Pro
               3065                   3070                   3075
Ala Pro Val Leu Arg Pro Leu Ser Arg Pro Gly Ser Gln Glu Cys
               3080                   3085                   3090
Met Asp Ala Ala Pro Gly Arg Leu Glu Pro Lys Asp Arg Gly Ser
               3095                   3100                   3105
Thr Leu Pro Arg Arg Gln Pro Pro Arg Asp Tyr Pro Gly Ala Met
               3110                   3115                   3120
Ala Gly Arg Phe Gly Ser Arg Asp Ala Leu Asp Leu Gly Ala Pro
               3125                   3130                   3135
Arg Glu Trp Leu Ser Thr Leu Pro Pro Arg Arg Thr Arg Asp
               3140                   3145                   3150
Leu Asp Pro Gln Pro Pro Pro Leu Pro Leu Ser Pro Gln Arg Gln
               3155                   3160                   3165
Leu Ser Arg Asp Pro Leu Leu Pro Ser Arg Pro Leu Asp Ser Leu
               3170                   3175                   3180
Ser Arg Ser Ser Asn Ser Arg Glu Gln Leu Asp Gln Val Pro Ser
               3185                   3190                   3195
Arg His Pro Ser Arg Glu Ala Leu Gly Pro Leu Pro Gln Leu Leu
               3200                   3205                   3210
Arg Ala Arg Glu Asp Ser Val Ser Gly Pro Ser His Gly Pro Ser
               3215                   3220                   3225
Thr Glu Gln Leu Asp Ile Leu Ser Ser Ile Leu Ala Ser Phe Asn
               3230                   3235                   3240
Ser Ser Ala Leu Ser Ser Val Gln Ser Ser Ser Thr Pro Leu Gly
               3245                   3250                   3255
Pro His Thr Thr Ala Thr Pro Ser Ala Thr Ala Ser Val Leu Gly
               3260                   3265                   3270
Pro Ser Thr Pro Arg Ser Ala Thr Ser His Ser Ile Ser Glu Leu
               3275                   3280                   3285
Ser Pro Asp Ser Glu Val Pro Arg Ser Glu Gly His Ser
               3290                   3295
```

```
<210> 22
<211> 905
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1424691CB1

<400> 22
cccacgcgtc cgtgttagaa ctccaaaaag cactaaacat gtccattcga ttcagtggag 60
tagaacaaaa cctcaggatg aagtgaaagc agtccaactt gccattcaga cattattcac 120
caattcagat ggcaaccctg gaagcaggtc cgactcaagt gctgattgcc agtggttaga 180
tactctgagg atgcggcaga ttgcatccaa cacttcttta cagcgttccc agagcaatcc 240
tattctgggg tcaccgttct tctcacactt tgatggccag gattcctacg ctgctgctgt 300
gagacggccc caggtgccca ttaagtatca acagattaca cctgtgaacc agtccagaag 360
ctcgtctcct actcagtatg gactgaccaa aaacttctct tccctacatc tcaactctag 420
ggacagtggc ttttccagtg gcaatactga cacctcttca gagaggggtc gatactcaga 480
cagaagcagg aacaaatatg gacgtggtag tatatcactc aattcttctc ctagaggaag 540
atacagtgga aagagtcagc attccactcc ttcaagagga agataccctg gaaagttcta 600
cagggtttct cagtcagcac tcaatcctca ccagtcgcct gacttcaaga gaagccccag 660
ggacctccac caacccaaca ccataccagg gatgcctttg caccctgaga ctgactcaag 720
agccagtgaa gaggacagca aagtcagcga agggggctgg acaaaagtgg aataccggaa 780
aaagccccac aggccatctc ccgccaaaac caataaagag agagccagag gggaccaccg 840
tggatggaga aactttgat gaattgaact acatagcttt tctaagcagg ttaaaaaaaa 900
aaaaa                                                           905
```

<210> 23
<211> 2390
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1450801CB1

<400> 23
```
tgaccttggc accccgcttc ctgccaaacg ccctgatcag tgtggacttt gctgccaact 60
atctcaccaa gatctatggg ctcacctttg ccagaagcc aaacttgagg tctgtgtacc 120
tgcacaacaa caagctggca gacgccgggc tgccggacaa catgttcaac ggctccagca 180
acgtcgaggt cctcatcctg tccagcaact tcctgcgcca cgtgcccaag cacctgccgc 240
ctgccctgta caagctgcac ctcaagaaca acaagctgga gaagatcccc ccggggggcct 300
tgcagcgagc tggagcagcc tgcgcgagct atacctgcag aacaactacc tgactgacga 360
gggcctggac aacgagacct tctggaagct ctccagcctg gagtacctgg atctgtccag 420
caacaacctg tctcgggtcc cagctgggct gccgcgcagc ctggtgctgc tgcacttgga 480
gaagaacgcc atccggagcg tggacgcgaa tgtgctgacc cccatccgca gcctggagta 540
cctgctgctg cacagcaacc agctgcggga gcagggcatc cacccactgg ccttccaggg 600
cctcaagcgg ttgcacacgg tgcacctgta caacaacgcg ctggagcgcg tgcccagtgg 660
cctgcctcgc cgcgtgcgca ccctcatgat cctgcacaac cagatcacag gcattggccg 720
cgaagacttt gccaccacct acttcctgga ggagctcaac ctcagctaca accgcatcac 780
cagcccacag gtgcaccgcg acgccttccg caagctgcgc ctgctgcgct cgctggacct 840
gtcgggcaac cggctgcaca cgctgccacc tgggctgcct cgaaatgtcc atgtgctgaa 900
ggtcaagcgc aatgagctgg ctgccttggc acgagggggcg ctggcggca tggctcagct 960
gcgtgagctg tacctcacca gcaaccgact gcgcagccga gccctgggcc cccgtgcctg 1020
ggtggacctc gcccatctgc agctgctgga catcgccggg aatcagctca cagagatccc 1080
cgaggggctc cccgagtcac ttgagtacct gtacctgcag aacaacaaga ttagtgcggt 1140
gcccgccaat gccttcgact ccacgcccaa cctcaagggg atctttctca ggtttaacaa 1200
gctggctgtg ggctccgtgg tggacagtgc cttccggagg ctgaagcacc tgcaggtctt 1260
ggacattgaa ggcaacttag agtttggtga catttccaag gaccgtggcc gcttgggggaa 1320
ggaaaaggag gaggaggaag aggaggagga ggaggaagag gaaacaagat agtgacaagg 1380
tgatgcagat gtgacctagg atgatggacc gccggactct tttctgcagc acacgcctgt 1440
gtgctgtgag cccccactc tgccgtgctc acacagacac acccagctgc acacatgagg 1500
catcccacat gacacgggct gacacagtct catatcccca cccttccca cggcgtgtcc 1560
cacggccaga cacatgcaca cacatcacac cctcaaacac ccagctcagc cacacacaac 1620
taccctccaa accaccacag tctctgtcac accccacta ccgctgccac gccctctgaa 1680
tcatgcaggg aagggtctgc ccctgccctg gcacacacag gcacccattc cctcccctg 1740
ctgacatgtg tatgcgtatg catacacacc acacacaca acatgcacaa gtcatgtgcg 1800
aacagccctc caaagcctat gccacagaca gctcttgccc cagccagaat cagccatagc 1860
agctcgccgt ctgccctgtc catctgtccg tccgttccct ggagaagaca caagggtatc 1920
catgctctgt ggccaggtgc ctgccaccct ctggaactca caaaagctgg ctttttattcc 1980
tttcccatcc tatggggaca ggagccttca ggactgctgg cctggcctgg cccaccctgc 2040
tcctccaggt gctgggcagt cactctgcta agagtccctc cctgccacgc cctggcagga 2100
cacaggcact tttccaatgg gcaagcccag tggaggcagg atgggagagc cccctgggtg 2160
ctgctggggc cttggggcag gagtgaagca gaggtgatgg ggctgggctg agccagggag 2220
gaaggaccca gctgcaccta ggagacacct ttgttcttca ggcctgtggg ggaagttccg 2280
ggtgccttta tttttttattc ttttctaagg aaaaaaatga taaaaatctc aaagctgatt 2340
tttcttgtta tagaaaaact aatataaaag cattatccct aaaaaaaaaa      2390
```

<210> 24
<211> 1471
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1597872CB1

<400> 24
```
cttggctagg agcccgctgc gggccaggcg cgcggtgcgc aggcataccc gggtcgcggg 60
tgaacaccgc ggagccccgg gacttgcctg tcgttgctgg tggcggcatg gtcttctgtc 120
tgtcgagcga ggagccgcgc cgcccgctgc gaacgacatg gtccacttcc aggcctcgga 180
agtccagcag ctgctacaca acaagttcgt ggtcatcttg ggggactcca ttcagagggc 240
tgtgtacaag gacctggtgc tcttgctcca gaaagactca ctgctcacag ctgcccagct 300
gaaagccaag taccttgagg atgttctgga agagctgaca tatggacctg ccccggacct 360
```

```
ggtgatcatc aactcctgcc tctgggatct ctccagatat ggtcgctgct caatggagag 420
ctaccgggag aacctggagc gggtgtttgt gcgcatggac caagtattgc cagactcctg 480
cctgctggtg tggaacatgg cgatgcccct cggggaacgt atcactgggg gtttcctcct 540
gccagagctc cagcccctgg caggctccct gcggcgggat gtggttgaag ggaacttcta 600
cagtgctacg ctggccgggg accactgctt tgatgtccta gacctccact ttcacttccg 660
gcatgcagta cagcaccgtc atcgggatgg tgtccactgg gaccagcatg cacaccgcca 720
cctctcacac ctgcttctga cccatgtggc tgacgcctgg ggcgtggagc tgcccaagcg 780
tggctatccc cctgacccgt ggattgagga ctgggcagag atgaatcatc cattccaggg 840
aagccatagg cagaccccag acttcgggga gcacctggcc ttgctcccac ccccaccttc 900
ttctttgcct cctcccatgc cttttcccta cccgcttcct cagccctcgc cacctcccct 960
cttcccaccc ctgccccagg ataccccttt tttcccaggc cagcccttcc caccccatga 1020
attcttcaac tataatccag tggaggactt ctcgatgcca ccccacttag gatgtggccc 1080
tggagtgaac tttgtgcctg gccctctgcc acctccaatc cctggcccta atccccatgg 1140
tcagcactgg ggcccagtgg tccaccgggg gatgccacgc tatgttccta acagccccta 1200
ccatgtgcgg agaatggggg ggccctgcag gcagcggctc agacactcag agagactgat 1260
ccacacatac aaactggaca gacggcctcc tgcccattcg gggacatggc ctgggtagac 1320
tggatcttgg gctgggactg gatgtgccaa tggcccttca gggcctgcct ggcacctcag 1380
gtactgggct agggtgtctg ctatgcctgg tattgttctt gtccattgct gtcaccaata 1440
aaggcatgga agaacagagt gaaaaaaaaa a                                1471
```

```
<210> 25
<211> 3293
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1674661CB1


<400> 25
gcgagcgcgg gcaggcggcg acgcgggggc aggggtggac ggcggtcaga gccgaacgcg 60
agggcggcgc ccggggactg gagctgcgcg cataggaca gctggcctga agctcagagc 120
cggggcgtgc gccatggccc cacactgggc tgtctggctg ctggcagcaa ggctgtgggg 180
cctgggcatt ggggctgagg tgtggtgagaa ccttgtgccg cgtaagacag tgtcttctgg 240
ggagctggcc acggtagtac ggcggttctc ccagaccggc atccaggact tcctgacact 300
gacgctgacg gagcccactg ggcttctgta cgtgggcgcc cgagaggccc tgtttgcctt 360
cagcatggag gccctggagc tgcaaggagc gatctcctgg gaggccccg tggagaagaa 420
gactgagtgt atccagaaag ggaagaacaa ccagaccgag tgcttcaact tcatccgctt 480
cctgcagccc tacaatgcct cccacctgta cgtctgtggc acctacgcct ccagcccaa 540
gtgcacctac gtcaacatgc tcaccttcac tttggagcat ggagagtttg aagatgggaa 600
gggcaagtgt ccctatgacc cagctaaggg ccatgctggc cttcttgtgg atggtgagct 660
gtactcggcc acactcaaca acttcctggg cacggaaccc attatcctgc gtaacatggg 720
gccccaccac tccatgaaga cagagtacct ggccttttgg ctcaacgaac ctcactttgt 780
aggctctgcc tatgtacctg agactgtggg cagcttcacg ggggacgacg acaaggtcta 840
cttcttcttc agggagcggg cactggagtc cgactgctat gccgagcagg tggtggctcg 900
tgtggcccgt gtctgcaagg gcgatatggg gggcgcacgg accctgcaga ggaagtggac 960
cacgttcctg aaggcgcggc tggcatgctc tgccccgaac tggcagctct acttcaacca 1020
gctgcaggcg atgcacaccc tgcaggacac ctcctggcac aacaccacct tctttggggt 1080
ttttcaagca cagtgggggtg acatgtacct gtcggccatc tgtgagtacc agttggaaga 1140
gatccagcgg gtgtttgagg gccctataa ggagtaccat gaggaagccc agaagtggga 1200
ccgctacact gaccctgtac ccagccctcg gcctggctcg tgcattaaca actggcatcg 1260
gcgccacggc tacaccagct ccctggagct acccgacaac atcctcaact tcgtcaagaa 1320
gcacccgctg atggaggagc aggtgggggcc tcggtggagc cgcccctgc tcgtgaagaa 1380
gggcaccaac ttcacccacc tggtggccga ccgggttaca ggacttgatg gagccaccta 1440
tacagtgctg ttcattggca caggagacgg ctggctgctc aaggctgtga gcctggggcc 1500
ctgggttcac ctgattgagg agctgcagct gtttgaccag gagcccatga gaagcctggt 1560
gctatctcag agcaagaagc tgctctttgc cggctcccgc tctcagctgg tgcagctgcc 1620
cgtggccgac tgcatgaagt atcgctcctg tgcagactgt gtcctcgccc gggacccta 1680
ttgcgcctgg agcgtcaaca ccagccgctg tgtggccgtg ggtggccact ctggatctct 1740
actgatccag catgtgatga cctcggacac ttcaggcatc tgcaacctcc gtggcagtaa 1800
gaaagtcagg cccactccca aaaacatcac ggtggtggcg ggcacagacc tggtgctgcc 1860
ctgccacctc tcctccaact tggtccatgc ccgctgacc tttggggcc gggacctgcc 1920
tgcggaacag cccgggtcct tcctctacga tgcccggctc caggccctgg ttgtgatggc 1980
tgcccagccc cgccatgccg gggcctacca ctgcttttca gaggagcagg gggcgcggct 2040
ggctgctgaa ggctaccttg tggctgtcgt ggcaggcccg tcggtgacct tggaggcccg 2100
ggcccccctg gaaaacctgg ggctggtgtg gctggcggtg gtggccctgg gggctgtgtg 2160
cctggtgctg ctgctgctgg tgctgtcatt gcgccggcgg ctgcgggaag agctggagaa 2220
```

```
aggggccaag gctactgaga ggaccttggt gtacccctg gagctgccca aggagcccac 2280
cagtcccccc ttccggccct gtcctgaacc agatgagaaa ctttgggatc ctgtcggtta 2340
ctactattca gatggctccc ttaagatagt acctgggcat gcccggtgcc agcccggtgg 2400
ggggcccct tcgccacctc caggcatccc aggccagcct ctgccttctc caactcggct 2460
tcacctgggg ggtgggcgga actcaaatgc caatggttac gtgcgcttac aactaggagg 2520
ggaggaccgg ggaggggctcg ggcaccccct gcctgagctc gcggatgaac tgagacgcaa 2580
actgcagcaa cgccagccac tgcccgactc caaccccgag gagtcatcag tatgaggga 2640
accccaccg cgtcggcggg aagcgtggga ggtgtagctc ctacttttgc acaggcacca 2700
gctacctcag ggacatggca cgggcacctg ctctgtctgg gacagatact gcccagcacc 2760
cacccggcca tgaggacctg ctctgctcag cacgggcact gccacttggt gtggctcacc 2820
agggcaccag cctcgcagaa ggcatcttcc tcctctctgt gaatcacaga cacgcgggac 2880
cccagccgcc aaaactttc aaggcagaag tttcaagatg tgtgtttgtc tgtatttgca 2940
catgtgtttg tgtgtgtgtg tatgtgtgtg tgcacgcgcg tgcgcgcttg tggcatagcc 3000
ttcctgtttc tgtcaagtct tcccttggcc tgggtcctcc tggtgagtca ttggagctat 3060
gaaggggaag gggtcgtatc actttgtctc tcctacccc actgccccga gtgtcgggca 3120
gcgatgtaca tatgcgaggtg gggtggacag ggtgctgtgc cccttcaaaa ggaagtgcaa 3180
ggccttgggg tgggcctagt cttgctcctt agggctgtga atggttttca gaggttgggg 3240
gaaggaaatt ggaaccctcc tgtgtgtttt gggggggaaa gggttggttg ggg     3293
```

```
<210> 26
<211> 1324
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1689337CB1

<400> 26
cagaatatca gatgtccaac atttcccttc tggctctttt tagctcccaa gtatctgctt 60
ccttaaaggc cctgagtcac ttcttctctc tttgcttcag actggcccgg gagcaagcgc 120
gagtgtgcga actgcagagt gggaaccagc agctggagga gcagcgggtg gagctggtgg 180
aaagactgca ggccatgctg caggcccact gggatgaggc caaccagctg ctcagcacca 240
ctctccgcc gcccaacct ccagctcctc ctccagcccc gggcctcagg 300
agcccgagaa ggaggagagg agggtctgga·ctatgcctcc catggccgtg gccctgaagc 360
ctgtattgca gcagagccgg gaagcaaggg acgagctacc tggagcgcct cctgttcttt 420
gcagttcctc ctcagatctt agcctcctgt tgggcccctc ttttcagagc cagcattctt 480
tccagcccct ggagcccaaa ccagacctca cttcatccac agctggggcc ttctctgcac 540
ttggggcctt ccatcccgat cataggggcag aaaggccatt ccctgaggaa gatcctggac 600
ctgacgggga gggcctccta aagcaagggc tgccgcctgc tcagctggag ggcctcaaga 660
attttttgca ccagttgctg gagacagtgc cccagaacaa tgagaaccct tctgtcgacc 720
tgttgcccc taagtctggt cctctgactg tcccatcttg ggaggaagcc cctcaagtgc 780
cacgtattcc accgcctgtc cacaaaacca aagttccctt agccatggca tccagtcttt 840
tccgggtccc tgagcctccc tcctcccatt cacaaggcag tggtcccagc agtggttccc 900
cagagagagg tggagatggg cttacattcc caaggcagct gatggaggtg tctcaactgt 960
tgcgactcta ccaggctcgg ggctggggg ctctgcctgc tgaggatctc ctgctctacc 1020
tgaagaggct ggaacacagc ggcaggactg atggccgagg ggataatgtc cccagaagga 1080
acacagactc ccgcttgggt gagatccccc ggaaagagat tccctcccag gctgtccctc 1140
gccgccttgc tacagcccc aagactgaaa aacctcccgc acggaagaaa agtgggcacc 1200
ctgccccgag tagcatgagg agccggggg gagtctggag atgagccccc ctaccctctc 1260
tcctctttgt tctctcattg ttgttatttt aataaatgct cagtagtctg taaaaaaaaa 1320
aaaa                                                           1324
```

```
<210> 27
<211> 1884
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1746392CB1

<400> 27
cgagggggtg tggaaactta ccggctgagc catggataca ccgttaaggc gcagccgacg 60
gctgggaggc ctaaggcccg aatcccccga gagcctcacc tcagtttcgc ggacgagacg 120
ggcccttgtg gagttcgagt cgaacccaga agaaacgagg gagcccgggt ctcctccgag 180
tgtgcagcgg gctggcctgg ggtcccccga aaggccgccg aagacaagcc caggatcacc 240
```

```
ccgtctgcag caggggtgcag gcttggagtc accccaaggg cagccagagc caggcgcagc 300
gtcccccccag cgtcagcaag acctacacct ggagtcgcct caaagacagc cagagtacag 360
tcctgaatcc ccacgatgtc agccgaagcc aagtgaggag gcaccgaagt gttctcagga 420
ccagggagta ctggcctcgg agttggccca gaataaggag gagctgaccc cggggggcccc 480
ccagcatcag ctaccgccgg tcccaggatc accagagcct taccccggtc agcaagctcc 540
cggtccggag ccctctcagc cactactgga gctgacaccc agggcacctg gctcccccccg 600
gggtcagcat gagccgagca agccacctcc agctggggag acggtgacag gcggcttcgg 660
ggcaaagaag cgaaaaggtt cttcatccca ggccccagcg tccaagaagt tgaataaaga 720
ggagcttcct gtaatcccga aggggaagcc caaatcgggg cgagtgtgga aggaccgctc 780
caagaaaaga ttctcccaga tgcttcagga caagcccctg cgcacatcgt ggcagcggaa 840
gatgaaggaa cgacaggaga ggaagctggc caaggacttt gcccgtcacc tggaggagga 900
gaaggagagg cgccgccagg agaagaaaca gcgccgggct gagaacctga aacgccgcct 960
ggagaatgag cggaaggcag aggtcgtcca agtgatccga aaccccgcca agctcaagcg 1020
ggcaaagaag aagcagctgc gctccattga gaagcgggac accctggccc tgctgcagaa 1080
gcagccgccc cagcagccgg cagccaagat ctgagctcag gacggcccga gggccttcca 1140
tggccaacaa acatgtcaga cacagcacct caggccgctg ctcagatgcc tctgctggag 1200
ctggcactcc aaacccatgg ctccagaaca gggaccccca ccccgaccgg ggctcctcgg 1260
cctttgaagg cttccaggca ggtctgtgtg ggacagaagc ccagagggggg cctgggacct 1320
ggcagagatg gggggcgggaa gagattcagc tcccatccct ccttcctctc cttctccaag 1380
tgccttcaaa ccaagaactg tacattcttc tggttcctca gtgagctggt gactggcagg 1440
tgactccctc agcagtgtat gccctttctc agcatcctag gtccatccca ggcctggagg 1500
ctgacagttg ggaatccagc ttcccccaca ccttcccaaa ggctgctctg agcacctcca 1560
cacccactg cctctgtccc cagcaaactg aatccggttc ctctccactt ttcaatactg 1620
aaaagattaaa atggggaggt tgcagggagc agagctttttc cctagcaccc actttcccaa 1680
accagtctct gcagaagccc cagagaatct aactcatgcc tgtccagtct acagcaaaaa 1740
tatttattga gtgcctgttg catacaggca caatcctagg caccggcaaa tacagacaat 1800
agaccaaagt ccctgccctc gaggagcttt cattctgatg gagagaaaac ataataaaca 1860
agcaaaatgc acaaaaaaaa aaaa                                       1884
```

```
<210> 28
<211> 2429
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1825182CB1

<400> 28
cctatttccaa aaaagctcga ctggagtgtt ataaaacctg aaaattctct tgtgctttct 60
cttcttttgc ttctagttac catcctcaaa ggattggcta aaagcaagca actggattga 120
acacccctaag aagaaagatt cacactgcac caggagacat cagaaagaat gaaaactctg 180
ccgctgtttg tgtgcatctg tgcactgagt gcttgcttct cgttcagtga aggtcgagaa 240
agggatcatg aactacgtca cagaaggcat catcaccaat cacccaaatc tcactttgaa 300
ttaccacatt atcctggact gctagctcac cagaagccgt tcattagaaa gtcctataaa 360
tgtctgcaca aacgctgtag gcctaagctt ccaccttcac ctaataagcc cccaaattc 420
ccaaatcctc accagccacc taaacatcca gataaaaata gcagtgtggt caaccctacc 480
ttagtggcta caacccaaat tccatctgtg actttcccat cagcttccac caaaattact 540
acccttccaa atgtgacttt tcttccccag aatgccacca ccatatcttc aagagaaaat 600
gttaacacaa gctcttctgt agctacatta gcaccagtga attccccagc tccacaagac 660
accacagctg ccccacccac accttctgca actacaccag ctccaccatc ttcctcagct 720
ccaccagaga ccacagctgc cccacccaca ccttctgcaa ctacacaagc tccaccatct 780
tcctcagctc caccagagac cacagctgcc ccacccacac ctcctgcaac tacaccagct 840
ccaccatctt cctcagctcc accagagacc acagctgccc cacccacacc ttctgcaact 900
acaccagctc cactatcttc ctcagctcca ccagagacca cagctgtccc acccacacct 960
tctgcaacta ccctagaccc atcatccgcc tcagctccac cagagaccac agctgcccca 1020
cccacacctt ctgcaactac accagctcca ccgtcttccc cagctccaca agagaccaca 1080
gctgccccaa ttaccacacc taattcttcc ccaactactc ttgcacctga cacttctgaa 1140
acttcagctg cacccacaca ccagactact acttcggtca ctactcaaac tactactact 1200
aaacaaccaa cttcagctcc tggccaaaat aaaatttctc gatttctttt atatatgaag 1260
aatctactaa acagaattat tgacgacgtg gtggagcaat agtatattgt atgttgtaaa 1320
gtgttctgtc atttacaaga tgtgattcat gagtgcagaa ctaccacctt tctttttagca 1380
ccaatcccaa catgaaatta tattactcag atttaaagca ctatcattaa tctttcaatc 1440
taattattca ccaccacaag acctattaac aagacaaaat gcctctatcc cacaagccag 1500
atgcaggtct ggggttcaaa ataactcttt ggatcctaca gagatagcct actgagggca 1560
gagaaagtcc ttagataaag agagaatatt gtatgggcca tcaaccattt acttttccct 1620
gaatgttaga aactacaaaa ccactacctt gtaccccat caaaatccca cctgaaccat 1680
```

```
ctaatcctat aaacataaag gggtaaaatt ggaactctcc agatgaacaa agacatctaa 1740
atatctgtag atagaaacat ttatctatct aaatatattg atagacctgt cattgtattg 1800
attaatgaca aaacccttta gataattatc ttccatttta aataaaattt tatttcacaa 1860
atatgagcca agaaagagga aagttgattt gaagtgagga ttagaagtga atgacaataa 1920
agtctggcag ccaagcacga accaagactg gcactatttt tcttagtgta tataattgtt 1980
taaactgcaa ggttgacatt tattgtgttg tgtctaagtt aattttgatc taatgtacct 2040
gattctagcc tctgtgaaca acaagaatat gtttgtgtat gttcacatgg tgcttataat 2100
atttcactat caattcaatt aattcacata aattccatgt gaaatgtatt caacaatgga 2160
atattttcta aaacatttag tatacatttg aatgtatttt aaaccatgcc aaactactgc 2220
tttaatgtca agtttgcaga attgtctctg aaaataaaaa ccctgacttt agttgtaaaa 2280
caataaaagt tagctacttg gtatacggag atgttaattt gggatatgga ggcattttta 2340
tcttctgtca ctactactta aaactctgat gattatgtta gatttttttg ctaactaata 2400
aagatttcaa atggcaattt ataaaaaaa                                    2429
```

<210> 29
<211> 985
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2155541CB1

<400> 29
```
ggaagagggc ggcgacggtg gtggtgactg agcggagccc ggtgacagga tgttggtgtt 60
ggtattagga gatctgcaca tcccacaccg gtgcaacagt ttgccagcta aattcaaaaa 120
actcctggtg ccaggaaaaa ttcagcacat tctctgcaca ggaaaccttt gcaccaaaga 180
gagttatgac tatctcaaga ctctggctgg tgatgttcat attgtgagag gagacttcga 240
tgagaatctg aattatccag aacagaaagt tgtgactgtt ggacagttca aaattggtct 300
gatccatgga catcaagtta ttccatgggg agatatggcc agcttagccc tgttgcagag 360
gcaatttgat gtggacattc ttatctcggg acacacacac aaatttgaag catttgagca 420
tgaaaataaa ttctacatta atccaggttc tgccactggg gcatataatg ccttggaaac 480
aaacattatt ccatcatttg tgttgatgga tatccaggct tctacagtgg tcacctatgt 540
gtatcagcta attggagatg atgtgaaagt agaacgaatc gaatacaaaa aaccttaaag 600
ccaggcctgt cttgatgatt tttggttttt tttcattgtc ctgttgaaat caagtaatta 660
aacatttaag agccacaaaa ttgtatcact tttataatat tttgcagtaa aatataatac 720
catcttctct gttaatacat aattgctcca agcttcctgt aaactataag aatatattta 780
gtttacagta tatggattct atgaaaaaat gtccacaaca cagtaattgg tcacttgtta 840
agaaaaattt atccttgtaa gtatcttcaa agttgatatt tggaacttta ttccaaaagt 900
agtgcatgtg gagaaagaat ctagactttc ttgtatacat ttttctcttc tccagtaata 960
aacaattacc tttcatttaa aaaaa                                         985
```

<210> 30
<211> 3381
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2215706CB1

<400> 30
```
gttagctcag tgtaacattg atgagctgaa gaaagagatg aatatgaatt ttggagactg 60
gcaccttttc agaagcacag tactagaaat gagaaacgca gaaagccacg tggtccctga 120
agacccacgt ttcctcagtg agagcagcag tggcccagcc ccgcacggtg agcctgctcg 180
ccgcgcttcc cacaacgagc tgcctcacac cgagctctcc agccagacgc cctacacact 240
caacttcagc ttcgaagagc tgaacacgct tggcctggat gaaggtgccc ctcgtcacag 300
taatctaagt tggcagtcac aaactcgcag aaccccaagt ctttcgagtc tcaattccca 360
ggattccagt attgaaattt caaagcttac tgataaggtg caggccgagt atagagatgc 420
ctatagagaa tacattgctc agatgtccca gttagagggg ggccccgggt ctacaaccat 480
tagtggcaga tcttctccac atagcacata ttacatgggt cagagttcat caggggggctc 540
tattcattca aacctagagc aagaaaaggg gaaggatagt gaaccaaagc ccgatgatgg 600
gaggaagtcc tttctaatga agaggggaga tgttatcgat tattcatcat caggggtttc 660
caccaacgat gcttccccccc tggatcctat cactgaagaa gatgaaaaat cagatcagtc 720
aggcagtaag cttctcccag gcaagaaatc ttccgaaagg tcaagcctct tccagacaga 780
tttgaagctt aagggaagtg ggctgcgcta tcaaaaactc ccaagtgacg aggatgaatc 840
tggcacagaa gaatcagata acactccact gctcaaagat gacaaagaca gaaaagccga 900
```

```
agggaaagta gagagagtgc cgaagtctcc agaacacagt gctgagccga tcagaacctt 960
cattaaagcc aaagagtatt tatcggatgc gctccttgac aaaaaggatt catcggattc 1020
aggagtgaga tccagtgaaa gttctcccaa tcactctctg cacaatgaag tggcggatga 1080
ctcccatctt gaaaaggcaa atctcataga gctggaagat gacagtcaca gcggaaagcg 1140
gggaatccca catagcctga gtggcctgca agatccaatt atagctcgga tgtccatttg 1200
ttcagaagac aagaaaagcc cttccgaatg cagcttgata gccagcagcc ctgaagaaaa 1260
ctggcctgca tgccagaaag cctacaacct gaaccgaact cccagcaccg tgactctgaa 1320
caacaatagt gctccagcca acagagccaa tcaaaatttc gatgagatgg agggaattag 1380
ggagacttct caagtcattt tgaggcctag ttccagtccc aacccaacca ctattcagaa 1440
tgagaatcta aaaagcatga cacataagcg aagccaacgt tcaagttaca caaggctctc 1500
caaagatcct ccggagctcc atgcagcagc ctcttctgag agcacaggct ttggagaaga 1560
aagagaaagc attctttgag aaaaacaagc aaaggagaag agtgttactg taccettatg 1620
acagaattgt cctggatttt gactccatcc acgcccatca cctttctaca ttttgctgac 1680
agataactaa ccgatgatga ggccgaggta aaagagacat ctgcagtgtg acagaaggga 1740
gcatgagaag catggctcac cagccagcct ctgtggtctt tgtaattaga agcttcagaa 1800
ctcactaata ctactgtacc tttcattggc gcattacccc ataaaacttt ttgagacgag 1860
gtgagatctg agtataaaga taggtcagaa gtattttaaa gggcttaatg tgccaaaaag 1920
aaaaaaagct agagaccctt tttgcaaaca tttggtgacc acacatttga gggaagacgt 1980
ggcgttaggt gaagcagaag caaaccctgc tcttagggggc tcacctaggt gagtgcacag 2040
cctgtgacgc tacagggaga ggctgagtaa accgagatcc agcgttctgt atggcagggg 2100
tattgcttat cacagaggtt ctgaagagta ggaagtacat aatgaagagg gctttaaaaa 2160
ttgccaacaa agtgagtcac cagggctggc agtagtgtga cggggctgtc ctgagctgtt 2220
aggagagtag atgcggggag ggctggtgac ctccgtgggt ttatatgtcg gaaactcttc 2280
tctccaaatc ccaggcctgg cttccagcac catccagctg tgcccaagaa gccaccctgg 2340
tctgttctcc aactctttta aatggtgccc aactttttcta agtgagctta gcaatgagaa 2400
gaaaaaaaaa catgaattct ttttctggaa aatcagggag acatgggtaa taataggtac 2460
taataaatat ttatagatga gtgaatgagg aaataattac atcaaaaagg tcagtgacaa 2520
ttgataaatg acaaggaaat atttaattag gtaaaactaa atcattgctc tctatactag 2580
gatagacttt atctacttca tctgttccta agtcagcatg ttagttctgg ggaaggatca 2640
taagaaagga aatacttttt aaaaaaaaat ttggaaacat gtaacaaagc aagggtaaaa 2700
tatatatata tatctatata agtgctgtga ctgtaaaagt gtactttcca ttaattatta 2760
gccgagttaa gagaatggtc acattgaagt actgtgtgga ctagaaatgt accctgtcat 2820
catgcaatga aatattgtta tcgtttttaac atagctcatt tatgtagaat gaattctggt 2880
ggtttacccc aagtcacagt taggacggta gatggtgaga tcgcagatgc gctattatct 2940
agattcagtg ttacattttc gatgtttatc actcagtggg tttttattaa tatgctgatt 3000
aagttattta ctgggccagt cattgtgcta aatagttgct cttttgtgtt tcattgcctt 3060
gatgtttgag tgtaatctag cattttaata cagtgtttat tttgcatgat ctttaacaaa 3120
tgttttaagc aattttaaaa aggcaggatg ttattgacat tatacactga agtcttaaca 3180
ttttaacatt tatagtgctt atttgcaaaa ttgtataatt aggaattatt tcagagacaa 3240
tgttttcttt ttcaggtgag tagttgccgc gtaatatcat tggagtacat tctttatact 3300
gtttgtgaaa ttaatactag catattaagt gtacaaatag atttagaaaa caataaaaaa 3360
ttgcatgcta aaaaaaaaaa a                                            3381
```

```
<210> 31
<211> 1803
<212> DNA
<213> Homo sapiens
```

```
<220>
<221> misc_feature
<223> Incyte ID No: 2347692CB1
```

```
<400> 31
gggctgttcc cggggaggct gtgatgggtt gacaggtgcg tgacagtggg agctgctctc 60
ggcacaagca tgtacggcaa aggcaagagt aacagcagcg ccgtcccgtc cgacagccag 120
gcccgggaga agttagcact ctacgtatat gaatatctgc tccatgtagg agctcagaaa 180
tcagctcaaa cattttatc agagataaga tgggaaaaaa acatcacatt gggggaacca 240
ccaggattct acattcttg gtggtgtgta ttttgggatc tctactgtgc agctccagag 300
agacgtgaaa catgtgaaca ctcaagtgaa gcaaaagcct tccatgatta cagtgctgca 360
gcagctccca gtccagtgct aggaaacatt cccccaggag atggcatgcc agtaggtcct 420
gtaccaccag ggttctttca gcctttttatg tcacctcggt accctggagg tccaaggccc 480
ccattgagga tacctaatca ggcacttgga ggtgtcccag gaagtcagcc attactcccc 540
agtggaatgg atccaactcg acaacaagga catccaaata tgggtgggcc aatgcagaga 600
atgactcctc caagaggaat ggtgcccta ggaccacaga actatggagg tgcaatgaga 660
cccccactga atgctttagg tggcctgga atgcctggaa tgaacatggg tccaggtggt 720
ggtagacctt ggccaaaccc aacaaatgcc aattcaatac catactcctc agcatctcct 780
gggaattatg taggtcctcc aggaggtgga gggccaccag gaacacccat catgcctagt 840
```

```
ccagcagatt caaccaactc tggtgataac atgtatactt taatgaatgc agtacctcct 900
ggacctaaca gacctaattt tccaatgggt cctgggtcag atggtcccat gggtggatta 960
ggaggaatgg agtcacatca catgaatggc tctttaggct caggagatat ggacagtatt 1020
tccaagaatt ctcccaataa tatgagcctg agtaatcaac cgggcactcc aagggatgat 1080
ggcgaaatgg ggggaaattt cttaaatcct tttcagagtg agagttactc ccctagcatg 1140
acaatgagcg tgtgatccat taccaagtct cctcatgaaa accacagtga gtcagccctt 1200
cacagaacta ctacggaaga aaattattca tcacagtgta cagttaaaca aaggaatctc 1260
agtcacacca aaccaacctt tttatttcct gctctctccc ctctttttgtg aagacagcgg 1320
gtccaaatgt gattcaaaca actgtacgga gtggcatatt agaattgccc taaactgaac 1380
tgcaaataat tatgtgtgta tgtatatgtg tgggaaagag aatgtactgt atatgtgtat 1440
gttatacaga catatacaca tacatacatt gacccacagg acattgtaaa atattatcac 1500
atgacatctt aagtagaaat aagtagggac ttttattcca tccttttttt cacgtttaca 1560
ttttaattat tacaagttgc tcctgccccc tccctgaact attttgtgct gtgtatatca 1620
ctgctttata taagttatttt tttaaggtga actcagatgt tatggttttg taaatgtctg 1680
caatcatgga taggaataaa atcgcttatt tgagagcttt cattaaattg cgtctgatgc 1740
aagttatcct gtgaatcaca aagtgtactg tctcaaaaaa tagaagaaaa tgtgaaaaaa 1800
aaa                                                              1803
```

```
<210> 32
<211> 1515
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2579048CB1

<400> 32
ggtaaagtgg cttctgggcg gaaggtacac tataggctcg gggaggtaag cggcggcagg 60
ccggcggttg gtgtgtcccg ggtgtggggga ggcgacagag ccctggcact tgagggttga 120
gggggcctcc ccagcgcggc gaaccgtcta gcctccggag gccaggccgt gagtgcggga 180
ggtatacgcc aaggcggaag aattttgcca ctcactacct gtgtgacctc gggtaaatta 240
gccttggaac gtcagtttct tcgtctctat aattgaaata ataatagtac ctctctcagg 300
attgttgtga gccgtcagtg aaacacttag agcagtttct ggcacatggt agaattgggc 360
tatttgctga agcttcttgg tggcccttgc tagcccagga agaaacttac attttgattt 420
ttttgtacca tggctttggt tcacaaattg ctgcatggta cttatttttct cagaaaattc 480
tctaagccaa cttctgcctt gtatccattt ttgggtattc tctttgcaga gtattccagt 540
agtcttcaga aaccagtggc ttctcctggc aaagcctcct cacagaggaa gactgaaggg 600
gatttgcaag gagatcacca gaaagaagtt gctttggata taacttcttc tgaggagaag 660
cctgatgtta gtttcgataa agcaattaga gatgaagcaa tataccattt taggcttttg 720
aaggatgaaa ttgtggatca ttggagagga ccggaaggcc accctctgca tgaggtcttg 780
ctggaacaag ccaaggttgt ctggcaattc cggggggaaag aagatttgga taagtggaca 840
gtgacttctg ataagacgat tggaggcaga agtgaagtgt ttttgaaaat gggcaagaat 900
aaccaaagtg cactgctata tggaactctg agctctgagg cgcctcagga cggggagtct 960
acccgaagtg ggtactgtgc aatgatatcc aggattccaa ggggtgcttt tgagaggaag 1020
atgtcttacg attggtccca gttcaatact ctgtatctcc gtgtacgtgg ggatggtcgg 1080
ccttggatgg tgaatatcaa ggaggacaca gatttcttcc agaggacgaa tcagatgtat 1140
agttacttca tgttcacccg cggggggaccc tactggcagg aggtcaagat tcctttttcc 1200
aaatttttct tctctaatcg aggaagaatc cgggatgttc agcatgagct tccgcttgat 1260
aagatctctt ctataggatt caccttggct gataaagtgg atggtccatt cttcctggag 1320
atagatttta ttggcgtgtt tactgatcca gctcatacag aagaatttgc ctatgaaaat 1380
tctccagagc ttaacccaag cttttttaaa taaagatcat atggtagttt tgtttttacta 1440
atctaagggt actagcatct acaatgatat agacaaaata aaatatttct ttaatggcat 1500
ccaaaaaaaa aaaaa                                                 1515
```

```
<210> 33
<211> 4416
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2604493CB1

<400> 33
cggatgggcg ggcagccgcg ccgccgcggc acttttttaa ttttttcggg tgccgcagcg 60
gcgacccctc ggcgccgatg tccctgatcc ctggagcgac gacggccgct gcctaagctg 120
```

```
gaaagaggaa tgccagctcc tgagcaggcc tcattggtgg aggaggggca accacagacc  180
cgccaggaag ctgcctccac tggcccaggc atggaacccg agaccacagc caccactatt  240
ctagcatccg tgaaggagca ggagcttcag tttcagcgac tcacccgaga actggaagtg  300
gaaaggcaga ttgttgccag tcagctagaa agatgtaggc ttggagcaga atcaccaagc  360
atcgccagca ccagctcaac tgagaagtca tttccttgga gatcaacaga cgtgccaaat  420
actggtgtaa gcaaacctag agtttctgac gctgtccagc ccaacaacta tctcatcagg  480
acagagccag aacaaggaac cctctattca ccagaacaga catctctcca tgaaagtgag  540
ggatcattgg gtaactcaag aagttcaaca caaatgaatt cttattccga cagtggatac  600
caggaagcag ggagtttcca caacagccag aacgtgagca aggcagacaa cagacagcag  660
cattcattca taggatcaac taacaaccat gtggtgagga attcaagagc tgaaggacaa  720
acactggttc agccatcagt agccaatcgg gccatgagaa gagttagttc agttccatct  780
agagcacagt ctccttctta tgttatcagc acaggcgtgt ctccttcaag ggggtctctg  840
agaacttctc tgggtagtgg atttggctct ccgtcagtga ccgacccccg acctctgaac  900
cccagtgcat attcctccac cacattacct gctgcacggg cagcctctcc gtactcacag  960
agaccgcct ccccaacagc tatacggcgg attgggtcag tcacctcccg gcagacctcc 1020
aatcccaacg gaccaacccc tcaataccaa accaccgcca gagtggggtc cccactgacc 1080
ctgacggatg cacagactcg agtagcttcc ccatcccaag gccaggtggg gtcgtcgtcc 1140
cccaaacgct cagggatgac cgccgtacca cagcatctgg gaccttcact gcaaaggact 1200
gttcatgaca tggagcaatt cggacagcag cagtatgaca tttatgagag gatggttcca 1260
cccaggccag acagcctgac aggcttacgg agttcctatg ctagtcagca tagtcagctt 1320
gggcaagacc ttcgttctgc cgtgtctccc gacttgcaca ttactcctat atatgagggg 1380
aggacctatt acagcccagt gtaccgcagc ccaaaccatg gaactgtgga gctccaagga 1440
tcgcagacgg cgttgtatcg cacaggttca ggtattggaa atctacaaag gacatccagc 1500
caacgaagta cccttacata ccaaagaaat aattatgctc tgaacacaac agctacctac 1560
gcggagccct acaggcctat acaataccga gtgcaagagt gcaattataa caggcttcag 1620
catgcagtgc cggctgatga tggcaccaca agatccccat caatagacag cattcagaag 1680
gaccccaggg agtttgcctg gcgtgatcct gagttgcctg aggtcattca catgcttcag 1740
caccagttcc catctgttca ggcaaatgca gcggcctacc tgcagcacct gtgctttggt 1800
gacaacaaag tgaagatgga ggtgtgtagg ttagggggaa tcaagcatct ggttgacctt 1860
ctggaccaca gagttttgga agttcagaag aatgcttgtg gtgcccttcg aaacctcgtt 1920
tttggcaagt ctacagatga aaataaaata gcaatgaaga atgttggtgg gatacctgcc 1980
ttgttgcgac tgttgagaaa atctattgat gcagaagtaa gggagcttgt tacaggagtt 2040
ctttggaatt tatcctcatg tgatgctgta aaaatgacaa tcattcgaga tgctctctca 2100
accttaacaa acactgtgat tgttccacat tctggatgga ataactcttc ttttgatgat 2160
gatcataaaa ttaaatttca gacttcacta gttctgcgta acacgacagg ttgcctaagg 2220
aacctcagct ccgcggggga agaagctcgg aagcaaatgc ggtcctgcga ggggctggta 2280
gactcactgt tgtatgtgat ccacacgtgt gtgaacacat ccgattacga cagcaagacg 2340
gtggagaact gcgtgtgcac cctgaggaac ctgtcctatc ggctggagct ggaggtgccc 2400
caggcccggt tactgggact gaacgaattg gatgacttac taggaaaaga gtctcccagc 2460
aaagactctg agccaagttg ctggggaag aagaagaaaa agaaaaagag gactccgcaa 2520
gaagatcaat gggatggagt tggtcctatc ccaggactgt cgaagtcccc caaaggggtt 2580
gagatgctgt ggcacccatc ggtggtaaaa ccatatctga ctcttctagc agaaagttcc 2640
aacccagcca ccttggaagg ctctgcaggg tctctccaga acctctctgc tggcaactgg 2700
aagtttgcag catatatccg ggcggccgtc cgaaaagaaa aggggctccc catccttgtg 2760
gagcttctga gaatggataa cgatagagtt gtttcttccg tggcaacagc cttgaggaat 2820
atggcactag atgttcgcaa caaggagctc ataggcaaat acgccatgcg agacctggtc 2880
aaccggctcc ccggcgggaa tggcccagt gtcttgtctg atgagaccat ggcagccatc 2940
tgctgtgctc tgcacgaggt caccagcaaa aacatggaga acgcaaaagc cctggccgac 3000
tcaggaggca tagagaagct ggtgaacata accaaaggca ggggcgacag atcatctctg 3060
aaagtggtga aggcagcagc ccaggtcttg aatacattat ggcaatatcg ggacctccgg 3120
agcatttata aaaaggatgg gtggaatcag aaccatttta ttacacctgt gtcgacattg 3180
gagcgagacc gattcaaatc acatccttcc ttgtctacca ccaaccaaca gatgtcaccc 3240
atcattcagt cagtcggcag cacctcttcc tcaccagcac tgttaggaat cagagaccct 3300
cgctctgaat acgataggac ccagccacct atgcagtatt acaatagcca aggggatgcc 3360
acacataaag gcctgtaccc tggtaagacg ccagttgggt gtgtgataca gtctcttgaa 3420
aagccgcatt tccaggcgct tggccagtgg cctgggaagt agcctgtgct tgtattgaga 3480
cagtccccca gcagcaaacc atgttccagt cattcccttt cctactttgg ggattgttgc 3540
cttttctgct tgtttaaagt aaaacaagca tgtacttgtt tgtatgtatg tatgtatgta 3600
gttgtacggt gggcacaaat aaaaagaggg ctgtatccaa ataaatcatt tctggctgct 3660
cactggcaca gtccctttgc tccgtcccct cctggctcga gcagtctctg tgttttccac 3720
atgcatcaga accgtcagcc cagtgtcact ttgcagggggc cacatcttct agactggctc 3780
atctcttaaa ttcaaaccag agaatggaga tcaatttcat ttacattttc atggagaaga 3840
gtttgaataa atagcaaaag gtataatgtg attcttctca acgtgattat tttttaagaa 3900
taacaaacaa aaataatgtt acatagtgtt aatatttta tatcctattc agaaagctgt 3960
gcatacaatt tatttaaagg ataccagccc aaagggttac taagatttca tactgttccc 4020
attctcaacc gtctggcgat tataactact ttagatgttc caaataagtc agtgtgagct 4080
acccacaaa aagtactctt ttctcaaacc tgtctattaa aaataaataa aagctggtgg 4140
```

34/42

```
cagctttact cctgctgggg gggcagtctc cattgtactg ttgtctttga aattgtgatt 4200
tcacaggact atttactaat cgactgttgt tactatggca attaatagct cagaaaattg 4260
cagatgctac atttcaacac caagctctgg gcaaaaggaa atgcacatac caactgaagt 4320
gcatggttgc ttccgatttg cagcagcctg ctttatctta cagatcacct ctttagcatg 4380
catgcccttc tgtatcttct tcgcttgctt caataa                          4416
```

```
<210> 34
<211> 4428
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2787182CB1

<400> 34
cggagggccg gggctgggtg gcagcggcca tggaccgctt cgtttggacc agcggcctcc 60
tggagatcaa cgagaccctg gtgatccagc agcgcggggt gcgaatctac gatggcgagg 120
agaagataaa atttgatgct gggactctcc ttcttagtac acaccgactg atttggagag 180
atcagaaaaa tcatgagtgt tgcatggcca ttctcctttc ccaaattgtg ttcattgaag 240
aacaggcggc tggaattggg aagagtgcca aaatagtggt tcatcttcac ccagctcctc 300
ctaacaaaga acctggccca ttccagagta gtaagaactc ctacatcaaa ctctccttca 360
aagaacatgg ccagattgag ttttacaggc gtttatcaga ggaaatgaca caaagaagat 420
gggagaatat gccagtttcc cagtcattac aaacaaatag aggaccccag ccaggaagaa 480
taagggctgt aggaattgta ggtattgaaa ggaaactgga agaaaaaaaa aaagaaactg 540
acaaaaacat ttctgaggcc tttgaagacc tcagcaaact aatgatcaag gctaaggaaa 600
tggtggaatt atcaaaatca attgctaata aaattaaaga caaacaaggt gacatcacag 660
aagatgagac catcaggttt aaatcctact tgctgagcat gggaatagct aacccagtta 720
ccagagaaac ctacggctca ggcacacagt accacatgca gctggccaaa caactggctg 780
gaatattgca ggtgccttta gaggaacgag ggggaataat gtcactcacg gaggtgtact 840
gcttagtaaa ccgagctcga ggaatggaat tgctctcacc agaagattta gtgaatgcgt 900
gcaagatgct ggaagcactg aaattacctc tcaggctccg tgtgtttgac agtggcgtca 960
tggtaattga gcttcagtct cacaaggaag aggaaatggt ggcctcggcc ctggagacag 1020
tttcagaaaa gggatcccta acatcagaag agtttgataa gcttgtggga atgtctgtcc 1080
tcctagccaa agaaaggttg ctgcttgcag agaagatggg ccatctttgc cgtgatgact 1140
cagtggaagg cctgcgtttt tacccaaatt tatttatgac acagagctaa gggtttttgta 1200
tttaaaatcc ttttttgtcca tatgcttgcg tcatgtagag gttgtatgac attgagctaa 1260
gagataaacc ccgatcaatt gagaatttat tagaacttca cagtgcaatg taaatctctt 1320
ttaatttctc actaaatatg gtccaggaaa tttatttagt atacgcatag gaaaattcag 1380
aaaagtgaat gccaatatga atttaaaatc atgctatagt gcagaaccct cagagtttaa 1440
cttggaatat agtggatttc aacttgatcc tcaaatctaa tcattttata aagaagggaa 1500
tttagttttg cagagaataa aaagagaagt tgcatgttca gacaggttag attattattt 1560
tggtgtaact gaaattcact gattgcacat gacaatgttg ggacaaaata tactgcagca 1620
tgctatatga ggctcctccc cagggctttt agaagcagtc atagacatgt cttcaacata 1680
ccaaataaaa taccttttaaa aatgaaataa ttttatttga cacatatatt tatatatatt 1740
ctatctagtt tctctttgtt tttttaagtg atgatttcat gactggcatt taaagaatgc 1800
aactgtgtca ttttgtttcc aaatgctgtg gattttgaaa ctgaactaga gagctgtata 1860
gacatgccca gagttatgat tacaaattta ggaggtagac ggctccaggaa ttccctggga 1920
ttgttgtgct ggtggaatgg cagagggaac ttcacaggaa ccttagtgtt cttttacctc 1980
aaagccacag acaggaaata gaaagtggaa aagtaatatc tccttttctt ttccataagg 2040
agtttcaaca ctgaacttta aaaagtctat catattccag caatattttt tctttgtcct 2100
ttatgttgta agttgtgtgg aaaaactact tcggtaagaa atgttactga gataacaaca 2160
actggctaat actgcatgta gattgcttag gttttaaagt gactgcctga cttcacatgt 2220
tattgctaca gcctccagta tgttcgcatt atctcaaact cagggacccc acaggacagg 2280
agacaccctt tctgaaactg agttggaagt gaaagggtgg tgatggtttt ggccaagcct 2340
gcgggaggga aagtattgta ttgggagcac ccttgggacc aggaagaggg atgcccaggt 2400
tcacactctg ggacccctaa gacattgtca gtgggtaagg tggagggcca ctgccagagg 2460
ctgctgcagt gccctctggg aagtgccagg gaccctcagc tgcagaccca ggggatccca 2520
atcccttatc tctgcctgaa aagtggctat tgctgcttcg tatcctccag tgtcacagga 2580
atgctgtgcc tgagacatcc cactttagtt tttgtttttcc aaacctgtca ctgactcttc 2640
attgtggtga cagatcctct ggttcccccca ttgctcagcc tcaggtttat tttgagggta 2700
actcagtgtc tgactgccca agtcttttag gggttagttg gaccattgtg taagcttgtt 2760
tgtatgtctc acctcttttct ggttggtact tactgtctca cactgctctg gcaaacttgt 2820
acacacacac acactctctc tctctctcac ctggctaagg cttttaaaat tatgaagata 2880
aataatctgt ttcaccagct ggagtgagtt gcaaggaaga ttgctggagc tactcaatct 2940
agcgctaatg gtttggattc attactgcaa acctacataa tttaacatat ttgtttactt 3000
tagtgtgaca actgatgaaa aaaaatggag caatctgaat tgtataaaat aacttaagaa 3060
```

```
ggaagaaaag tgatatataa atatattttg caaatgtcac attaatttaa aaatgagtat 3120
gattgatttt atttttaaag tgggcattct tcactgtttc gagacctttg tatgtatttg 3180
tgtattttta tctttttttt tcaggccatt attataaggt gttattttgg ccctctaatg 3240
tagaagttat gtttaaatac aaccaatcag gccctaagtg caaaaaagtt ctgtcttggt 3300
gcttatcact ggtataatta ttattttttt gttttcctaa ctttgctctt aggagcatga 3360
gcctctttgt agctttatgg taatgcaata tttctggtca tttactgtca aaaaattttt 3420
ttacattgtg ttagtgaaga ctgtgttttc agggttaaat gattggtatc aatgtatata 3480
gagtaaaatt attgcaaaat ttaaaaatga tttttcttgg cattcttttt aaatactctg 3540
aaacatatat gcaaatgaga aacctttaat catactaaag ccagttatgt taagaatttt 3600
tcctttggat tttataatta agagttgctt ataaatactt atgacattga gctcttactg 3660
ttttagttgt cttaaaagaa tgggacatgt catgaactgg tttctttttt taaaaaattc 3720
ttgatgtgaa ttccactgtt acctgaccat gtatattcag atgaatgtac tctttcttgt 3780
tccttgttac cagattaatc tgagagaatg tggattcatc ctgtcatctt tctcatactc 3840
aaatacttaa aatggttctt ttgcccaaaa gtctcagagt cttcattttg gtacagtgga 3900
gtcacaactt gtaaggtggt taggtttaa agaccgtgcc taaggacaaa attgagcatg 3960
ctcagaatgg tccttgaaaa tctcctaaat taccaataaa tttctctttg tagtcttaaa 4020
gtttaaatcc ctgtggagtg atatgtaggt atgaatatat tatgcttata ttaagtacaa 4080
aaatacaaac tgcatatcaa gagattctta tagcattaat aatttccatg catgtgtctt 4140
tttccagtag gtatggttga atttatgtaa atttattgct aatcccatcc cttacgatct 4200
agagtataag ctgcgcaagg gcagaagttt ttatctggtt tgttcatgga tgtattctaa 4260
gagctgagaa cagggcctgg acacaataag cattcaataa atatttactg aatgaatgaa 4320
ctcctaccta tattcctatt tataatttgg ctccactta tcctacttta gctcccattc 4380
aattcaataa aaaaaacatt tttttgaaca cataaaaaaa aaaaaaaa      4428
```

<210> 35
<211> 1907
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 3096668CB1

<400> 35
```
gcgttgctgc gtaaatggcg ggggcgtgtc ttttggctcc tccgcgtgta gttacctgag 60
aaacgcggga agttgggccc aggcagtgtt gctgcggttg cctaagttgt tttactattt 120
ctggagagag ccgtgagctt gtccaggggc cccaatcctg aggccgaccc ggtttctggc 180
gcggtgcgat ggaggtagtg gaggccgccg ccgctcagct ggaaactctg aaattcaatg 240
gcaccgactt tggagttggg gaaggtccgg cggctccgtc tccgggctct gccctgtgc 300
cagggacaca gccgccgcta cagtcgtttg aggggtcccc ggacgctggg cagaccgtgg 360
aggttaagcc tgccggggag cagcctctgc agcccgttct gaacgccgtc gcggccggga 420
ccccggcgcc gcagccacag ccaccggctg aatcgccggc ctgcggagac tgcgtcacct 480
ccccaggagc cgcagagcct gcgcgggcgc cggactcctt ggagacctcg gactcggatt 540
cggactcgga cagtgaaaca gattcagata gttcaagttc atcgtcttcc tcttcatctt 600
cctcatcgtc gtcttcttcc tcttgtatat cacttcctcc agtgctgtca gatggagatg 660
atgatttaca agttgagaag gaaaataaga attttcctct taaaacaaaa gatgaattac 720
ttcttaatct atagagaaaa aaaaaattca gtcatggctc tcagtactcc agggattgga 780
tcctactttc caaccatatc tgaaaagtga aggctcacct aatagcatca ggtaattggc 840
tgccacgtgc atgtcctgtg ttgggtaata tgagaaaagt ggttagataa tttcatccca 900
ccttcctcac ttttctcaat tctccccaaa ctgacaccaa aaaggtttag ttttcatttg 960
gaatgtttga ttccttctcc caccaacctc tgttgtcctt tttccatatt tgtgagtgaa 1020
aatcctactg aaagttcttt atataatttt actttagaaa gtcatcaatt tactgatact 1080
cttttttgct caataagcct tcacaaatgc ttgaaaagtc aacagtgtgg taaatgataa 1140
atgttacctt ttcagagggc cacttttgac atattagctt cttccatttt tgcattgaaa 1200
gtgttaggca cccattttt gactggtatg tctataacct cattttaat taggatggat 1260
tttttaatgt tatgtggtac tcttttgaat attttgctta actgaataac cttgtagacc 1320
atacagatgt tagaaaatta aaatataata atcttacaaa aacagacaat aattgctctt 1380
tcatggatat tccagaagtg tggttaggat cttgcatttc tttaatgcca tcgttacgag 1440
tatctgttat cacagaagca cagtaatttt tttattggga tctagtatat aatttctgta 1500
ttaatgtgtt gtcttttga ttacatgcag ttggacattt aaattgtcgt tagccatttg 1560
tgtaactgtt tagaactgt gctcagtttc cttactattc gtaggtaaga aaaatgaaac 1620
cagaaagaaa gagacttgtc tgaagtcata ttagtgggga ggagcagatc tgaactggta 1680
atagatacat tccaaactgc tgtgttttta gtatttgtgg agacctgcat agcaacgttg 1740
gaatctggtc gtttggactt tctcattatt tggtttctga ataatcatgt agcatatttt 1800
ctcaaagtga aggatgaatg tatcatctaa tgtaagcttt ttaaaattgt atttgcttgg 1860
attatattgc ctctcaataa agctttttgac ttggaaaaaa aaaaaaa      1907
```
```

<210> 36
<211> 1839
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 3143411CB1

<400> 36
gcggtccgtc ggtggcctag agatgctgct gccgcggttg cagttgtcgc gcacgcctct 60
gcccgccagc ccgctccacc gccgtagcgc ccgagtgtcg gggggcgcac ccgagtcggg 120
ccatgaggcc gggaaccgcg ctacaggccg tgctgctggc cgtgctgctg gtggggctgc 180
gggccgcgac gggtcgcctg ctgagtgggc agccagtctg ccggggaggg acacagaggc 240
cttgttataa agtcatttac ttccatgata cttctcgaag actgaacttt gaggaagcca 300
aagaagcctg caggagggat ggaggccagc tagtcagcat cgagtctgaa gatgaacaga 360
aactgataga aaagttcatt gaaaacctct tgccatctga tggtgacttc tggattgggc 420
tcaggaggcg tgaggagaaa caaagcaata gcacagcctg ccaggacctt tatgcttgga 480
ctgatggcag catatcacaa tttaggaact ggtatgtgga tgagccgtcc tgcggcagcg 540
aggtctgcgt ggtcatgtac catcagccat cggcacccgc tggcatcgga ggccctaca 600
tgttccagtg gaatgatgac cggtgcaaca tgaagaacaa tttcatttgc aaatattctg 660
atgagaaacc agcagttcct tctagagaag ctgaaggtga ggaaacagag ctgacaacac 720
ctgtacttcc agaagaaaca caggaagaag atgccaaaaa aacatttaaa gaaagtagag 780
aagctgcctt gaatctggcc tacatcctaa tccccagcat tccccttctc ctcctccttg 840
tggtcaccac agttgtatgt tgggtttgga tctgtagaaa aagaaaacgg gagcagccag 900
accctagcac aaagaagcaa cacaccatct ggccctctcc tcaccaggga aacagcccgg 960
acctagaggt ctacaatgtc ataagaaaac aaagcgaagc tgacttagct gagacccggc 1020
cagacctgaa gaatatttca ttccgagtgt gttcgggaga agccactccc gatgacatgt 1080
cttgtgacta tgacaacatg gctgtgaacc catcagaaag tgggtttgtg actctggtga 1140
gcgtggagag tggatttgtg accaatgaca tttatgagtt ctccccagac caaatgggga 1200
ggagtaagga gtctggatgg gtggaaaatg aaatatatgg ttattaggac atataaaaaa 1260
ctgaaactga caacaatgga aaagaaatga taagcaaaat cctcttattt tctataagga 1320
aaatacacag aaggtctatg aacaagctta gatcaggtcc tgtggatgag catgtggtcc 1380
ccacgacctc ctgttggacc cccacgtttt ggctgtatcc tttatcccag ccagtcatcc 1440
agctcgacct tatgagaagg taccttgccc aggtctggca catagtagag tctcaataaa 1500
tgtcacttgg ttggttgtat ctaactttta agggacagag ctttacctgg cagtgataaa 1560
gatgggctgt ggagcttgga aaaccacctc tgttttcctt gctctataca gcagcacata 1620
ttatcataca gacagaaaat ccagaatctt ttcaaagccc acatatggta gcacaggctg 1680
gcctgtgcat cggcaattct catatctgtt ttttttcaaag aataaaatca aataaagagc 1740
aggaaacaga aaaaaaaagg agatagggta gtagatgatg gtaaggagtg cttaagaagg 1800
tgtgggaaga gttgattgaa tggaggggggt cccttgttt                         1839

<210> 37
<211> 503
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 3170835CB1

<400> 37
cggctcgaga tgaaattcgc catcgtcctg ttcgccctct ttgccgtggc cctggctgcc 60
cctactgtcg aggtcctgcg atcggatagc aatgttggaa tcgataacta ctcatatgca 120
gttgaaacca gcgacggtac ctcgaagagc gaggagggtg tgctgaagaa cgccggcacc 180
gagctagagg ccatctcaac ccacggctcc ttcagctacg tgggccctga tggccagacc 240
tacaccgtca cctacgtggc cgatgagaac ggattccagc cccagggtgc tcatctgccc 300
gttgcccccg ttgcctaagc taaggagttg aaataaattg tttataaaag caaaaaaact 360
ggcagaaaga acccaaagta cgtagacctt catgctagag agaatgtgat gtctgccgaa 420
gacaaccgta cccgcctgcg caatcttacg gccactagtg gatcctgcgc atgaggacac 480
cgagagcgag cgtggggggg ggc                                           503

<210> 38
<211> 2154
<212> DNA
<213> Homo sapiens

```
<220>
<221> misc_feature
<223> Incyte ID No: 3550808CB1

<400> 38
gaggacagga tgaggcccgg cctctcattt ctcctagccc ttctgttctt ccttggccaa 60
gctgcagggg atttgggggga tgtgggacct ccaattccca gccccggctt cagctctttc 120
ccaggtgttg actccagctc cagcttcagc tccagctcca ggtcgggctc cagctccagc 180
cgcagcttag gcagcggagg ttctgtgtcc cagttgtttt ccaatttcac cggctccgtg 240
gatgaccgtg ggacctgcca gtgctctgtt tccctgccag acaccacctt tcccgtggac 300
agagtggaac gcttggaatt cacagctcat gttctttctc agaagtttga gaaagaactt 360
tctaaagtga gggaatatgt ccaattaatt agtgtgtatg aaaagaaact gttaaaccta 420
actgtccgaa ttgacatcat ggagaaggat accatttctt acactgaact ggacttcgag 480
ctgatcaagg tagaagtgaa ggagatggaa aaactggtca tacagctgaa ggagagtttt 540
ggtggaagct cagaaattgt tgaccagctg gaggtggaga taagaaatat gactctcttg 600
gtagagaagc ttgagacact agacaaaaac aatgtccttg ccattcgccg agaaatcgtg 660
gctctgaaga ccaagctgaa agagtgtgag gcctctaaag atcaaaacac ccctgtcgtc 720
caccctcctc ccactccagg gagctgtggt catggtggtg tggtgaacat cagcaaaccg 780
tctgtggttc agctcaactg gagagggttt tcttatctat atggtgcttg gggtagggat 840
tactctcccc agcatccaaa caaaggactg tattgggtgg·cgccattgaa tacagatggg 900
agactgttgg agtattatag actgtacaac acactggatg atttgctatt gtatataaat 960
gctcgagagt tgcggatcac ctatggccaa ggtagtggta cagcagttta caacaacaac 1020
atgtacgtca acatgtacaa caccgggaat attgccagag ttaacctgac caccaacacg 1080
attgctgtga ctcaaactct ccctaatgct gcctataata accgctttttc atatgctaat 1140
gttgcttggc aagatattga ctttgctgtg gatgagaatg gattgtgggt tatttattca 1200
actgaagcca gcactggtaa catggtgatt agtaaactca atgacaccac acttcaggtg 1260
ctaaacactt ggtataccaa·gcagtataaa ccatctgctt ctaacgcctt catggtatgt 1320
ggggttctgt atgccacccg tactatgaac accagaacag aagagatttt ttactattat 1380
gacacaaaca cagggaaaga gggcaaacta gacattgtaa tgcataagat gcaggaaaaa 1440
gtgcagagca ttaactataa ccctttttgac cagaaacttt atgtctataa cgatggttac 1500
cttctgaatt atgatctttc tgtcttgcag aagccccagt aagctgttta ggagttaggg 1560
tgaaagagaa aatgtttgtt gaaaaaatag tcttctccac ttacttagat atctgcaggg 1620
gtgtctaaaa gtgtgttcat tttgcagcaa tgtttaggtg catagttcta ccacactaga 1680
gatctaggac atttgtcttg atttggtgag ttctcttggg aatcatctgc ctcttcaggc 1740
gcattttgca ataaagtctg tctagggtgg gattgtcaga ggtctagggg cactgtgggc 1800
ctagtgaagc ctactgtgag gaggcttcac tagaagcctt aaattaggaa ttaaggaact 1860
taaaactcag tatggcgtct agggattctt tgtacaggaa atattgccca atgactagtc 1920
cccatccatg tagcaccact aattcttcca tgcctggaag aaacctgggg acttagttag 1980
gtagattaat atctggagct cctcgaggga ccaaatctcc aacttttttt tcccctcact 2040
agcacctgga atgatgcttt gtatgtggca gataagtaaa tttggcatgc ttatatattc 2100
tacatcctga aagtggcctg gttttatgga gaagaggcct ctttatgcag tcaa        2154
```

```
<210> 39
<211> 733
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 3683905CB1

<400> 39
gcgagcgagt tgccgagcgc gccccgtccc tcgcgcgcga tgctcccctg gacggcgctc 60
ggcctggccc tgagcttgcg gctggcgctg gcgcgggagcg gcgcgggagc gcggtccacc 120
agcatcagcc ccccgagggg acctgatgtt cctgctggac agctcagcca gcgtctctca 180
ctacgagttc tcccgggttc gggagtttgt ggggcagctg gtggctccac tgcccctggg 240
caccggggcc ctgcgtgcca gtctggtgca cgtgggcagt cggccataca ccgagttccc 300
cttcggccag cacagctcgg gtgaggctgc ccaggatgcg gtgcgtgctt ctgcccagcg 360
catgggtgac acccacactg gcctggcgct ggtctatgcc aaggaacagc tgtttgctga 420
agcatcaggt gcccggccag gggtgcccaa agtgctggtg tgggtgacag atggcggctc 480
cagcgaccct gtgggccccc ccatgcagga gctcaaggac ctggcgtca ccgtgttcat 540
tgtcagcacc ggccgaggcc acttcctgga gctgtcagcc gctgcctcag cccctgccga 600
gaagcacctg cactttgtgg acgtggatga cctgcacatc attgtccaag agctgagggg 660
ctccattctc gacgcgatgc ggccgcaagc ttattccctt tagtgagggt taattttagc 720
ttgcactggc cgt                                                    733
```

```
<210> 40
```

<211> 718
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 4062841CB1

<400> 40
gccggcgcca gggcaggcgg gcggctggca gctgtggcgc cgacatggct gcgctggtgg 60
agccgctggg gctggagcgg gacgtgtccc gggcggttga gctcctcgag cggctccagc 120
gcagcgggga gctgccgccg cagaagctgc aggccctcca gcgagttctg cagagccgct 180
tctgctccgc tatccgagag gtgtatgagc agctttatga cacgctggac atcaccggca 240
gcgccgagat ccgagcccat gccacagcca aggccacagt ggctgccttc acagccagcg 300
agggccacgc acatcccagg gtagtggagc tacccaagac ggatgagggc ctaggcttca 360
acatcatggg tggcaaagag caaaactcgc ccatctacat ctcccgggtc atcccagggg 420
gtgtggctga ccgccatgga ggcctcaagc gtggggatca actgttgtcg gtgaacggtg 480
tgagcgttga gggtgagcag catgagaagg cggtggagct gctgaaggcg cccagggct 540
cggtgaagct ggttgtccgt tacacaccgc gagtgctgga ggagatggag gcccggttcg 600
agaagatgcg ctctgcccgc cggcgccaac agcatcagag ctactcgtcc ttggagtctc 660
gaggttgaaa ccacagatct ggacgttcac gtgcactctc ttcctgtaca gtatttat 718

<210> 41
<211> 1235
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 6394358CB1

<400> 41
gccgccggag ccgccgccgc agcggggacg gggagccccc gggggccccg ccaccgccgc 60
cgtccgccgt cacctacccg gactggatcg gccagagtta ctccgaggtg atgagcctca 120
acgagcactc catgcaggcg ctgtcctggc gcaagctcta cttgagccgc gccaagctta 180
aagcctccag ccggacctcg gctctgctct ccggcttcgc catggtggca atggtggagg 240
tgcagctgga cgctgaccac gactacccac cggggctgct catcgccttc agtgcctgca 300
ccacagtgct ggtggctgtg cacctgtttg cgctcatgat cagcacctgc atcctgccca 360
acatcgaggc ggtgagcaac gtgcacaatc tcaactcggt caaggagtcc ccccatgagc 420
gcatgcaccg ccacatcgag ctggcctggg ccttctccac cgtctccac acgctgctct 480
tcctagctga ggtggtgctc ctctgctggg tcaagttctt gcccctcaag aagcagccag 540
gccagccaag gcccaccagc aagcccccg ccagtggcgc agcagccaac gtcagcacca 600
gcggcatcac cccgggccag gcagctgcca tcgcctcgac caccatcatg gtgcccttcg 660
gcctgatctt tatcgtcttc gccgtccact tctaccgctc actggttagc cataagactg 720
accgacagtt ccaggagctc aacgagctgg cggagtttgc ccgcttacag gaccagctgg 780
accacagagg ggaccacccc ctgacgcccg gcagccacta tgcctaggcc catgtggtct 840
gggccctttcc agtgctttgg ccttacgccc ttccccttga ccttgtcctg ccccagcctc 900
acggacagcc tgcgcagggg gctgggcttc agcaaggggc agagcgtgga gggaagagga 960
tttttataag agaaatttct gcactttgaa actgtcctcc aagagaataa gcatttcctg 1020
ttcttccagc tccaggtcca cctcctgttg ggaggcggtg gggggccaaa gtggggccac 1080
acactcgctg tgtcccctct cctccctgt gccagtgcca cctgggtgcc tcctcctgtc 1140
ctgtccgtct caacctccct cccgtccagc attgagtgtg tacatgtgtg tgtgacacat 1200
aaatatactc ataaggacac ctccaaaaaa aaaaa 1235

<210> 42
<211> 11648
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2847752CB1

<400> 42
atggcgaggc ggccgccgtg gcggggcctc gggggacggt cgaccccat actcctgctc 60
cttctcctct ctttgttccc cctcagccag gaggagctgg ggggcggtgg gcaccagggc 120
tgggacccag gcttagctgc cactacgggg ccaagggcgc atatcggtgg cggagcctta 180

39/42

```
gctctttgtc cggagtcttc cggggtccgg gaggatgggg ggcctggcct ggggggtcagg 240
gagcctatct tcgtgggggct ccgagggaga aggcaaagcg cccggaatag tcgagggccc 300
cctgagcagc cgaatgagga gctggggatt gaacacggcg tccagccatt gggcagccgc 360
gaacgagaga caggacaggg accagggtct gtgttatact ggcgcccaga ggtctcctct 420
tgcgggcgga caggaccttt gcaaagaggt agtctgtcac caggggctct gtcctcaggg 480
gtcccgggct cggggaacag ctcgcccctc ccttcagact ttttgattcg gcaccacggt 540
cccaagccgg tgtcctccca gcggaacgct gggacaggct cccgcaaaag agtgggcacc 600
gcgcgctgct gtggggaatt atgggcaaca gggagcaagg gtcagggcga gagagccacg 660
acatccggag cagaaaggac agcccccccgg cggaactgtc ttccaggggc ctcgggatct 720
ggccccgagc tggattcagc accacgcacg gcgaggacag ctcctgcatc aggttcagca 780
ccccgcgagt ctcggacagc tcccgagccg gcgcccaagc gcatgcgctc ccggggtctc 840
ttccgctgcc gcttcctccc gcagcgcccc gggccgcgtc ccccgggact cccggcccgt 900
cctgaagcca ggaaagtaac ctcggcgaac cgggcacgct ttcgtcgcgc cgcaaaccgc 960
caccccgcagt ttccgcagta caactaccag acgctggtgc cggagaatga ggcagcaggc 1020
accgcggtgc tacgcgtggt tgctcaggac ccggacgccg gcgaggccgg gcgcctagtc 1080
tactcgctgg cggcactcat gaacagccgc tcgctggagc tgttcagcat cgacccgcag 1140
agcggcctta tccgtacggc ggcagctctg gaccgcgaga gcatggagcg tcactacctg 1200
cgtgtgaccg cgcaggacca cgggtcgccg cgcctctcgg ccaccacgat ggtggccgtg 1260
acagtagccg accgcaacga ccactcgccg gtttttgagc aagcgcagta ccgggagacc 1320
cttcgcgaga atgtggagga gggctacccct atcctgccac tgcgtgccac tgacggcgac 1380
gcgcccccca acgccaacct gcgctaccgc ttcgtgggggc cgccagctgc gcgcgctgca 1440
gctgccgccg ccttcgagat tgatccacgc tccggcctca tcagcaccag cggccgagtg 1500
gaccgcgagc acatggaaag ctatgagctg gtggtggaag ccagcgacca gggccaggaa 1560
cccgggccgc gctcggccac tgtgcgcgta cacataactg tgctagacga gaacgacaat 1620
gctcctcagt tcagcgagaa gcgctacgtg gcgcaggtgc gcgaggatgt gcgcccccac 1680
acagtcgtgc tgcgcgtcac ggccactgac cgggacaagg acgccaacgg attggtgcac 1740
tacaacatca tcagtgggcaa tagccgtgga cactttgcca tcgacagcct cactggcgag 1800
atccaggtgg tggcacctct ggacttcgag gcagagagag agtatgccctt gcgcatcagg 1860
gcgcaggatg ctggccggcc accgctgtcc aacaacacgg gcctggccag catccaggtg 1920
gtggacatca atgaccacat tcctattttt gtcagcacgc ccttccaagt ttctgtcttg 1980
gaaaatgctc ccttgggtca ctcagtcatc cacattcagg cagtcgatgc agaccatggg 2040
gagaatgcca gattggagta ctccctaact ggtgtggcac ctgatactcc ttttgtgata 2100
aacagcgcca ctggctgggt ctctgtgagt ggtcccctgg accgtgagtc tgtggagcat 2160
tacttctttg gtgtggaggc tcgagaccat ggctcaccccc cactctctgc ctcagccagt 2220
gtcaccgtga ctgtgctgaca cgttaatgac aatcggcctg agttcacaat gaaggagtac 2280
cacctacgac tgaatgagga tgcagctgtg ggcaccagtg tggtcagcgt gaccgcagta 2340
gaccgtgatg ccaacagtgc catcagctac cagatcacag gcggcaacac ccggaatcgc 2400
tttgccatca gcacccaggg gggtgtgggt ctggtgactc tggctctgcc actggactac 2460
aagcaggaac gctacttcaa gctggtacta actgcatctg accgtgccct tcatgatcac 2520
tgctatgtgc acatcaacat cacagatgcc aacactcatc ggccggtctt tcaaagtgcc 2580
cactactcag tgagtgtgaa tgaagatcgg ccaatgggta gcaccatagt ggtcatcagt 2640
gcctctgatg atgacgtggg tgagaatgct cgtatcacct atctcctgga ggacaacctg 2700
ccccagttcc gcattgatgc agactcagga gccattacat tacaggcccc attagactat 2760
gaggaccagg tgacctacac cctggctatc acagctcggg acaatggcat cccacagaag 2820
gcagacacta cttatgtgga ggtgatggtc aatgacgtga atgacaatgc tccacaattt 2880
gtggcctccc actatacagg gctggtctct gaggatgccc caccttcac cagtgtcctg 2940
cagatctcag ccactgaccg ggatgctcat gccaatggcc gggtccagta cactttccag 3000
aatggtgaag atgggggatgg agattttacc attgagccca cctctggaat tgtccgtaca 3060
gtaaggcggc tagaccggga ggcagtatca gtgtatgagt tgactgccta cgcagtggac 3120
agaggtgtgc ccccactccg gactccagtc agtatccagg tgatggtgca ggatgtgaac 3180
gacaatgcac ctgtcttccc agctgaggag tttgaggtgc gggtgaaaga gaatagcatt 3240
gtgggctcag tggtggccca gatcactgca gtggaccctg acgaaggccc caatgcccat 3300
ataatgtacc agatcgtgga ggggaacatc cctgagctgt tccaaatgga catcttctct 3360
ggagaactga cggcactcat tgacctagac tatgaggctc gccaagaata tgtgattgtg 3420
gtgcaggcca catctgctcc tttggtcagc cgggccactg tgcacgtccg cctggttgac 3480
cagaatgaca acagccctgt gctcaacaac ttccagatcc tcttcaacaa ctatgtatcc 3540
aaccgttcag acaccttccc gtcgggcatt attgggcgca tcccagctta tgaccccgat 3600
gtctccgacc acctcttcta ctcctttgag cgtggcaatg agctgcagct gctggtagtc 3660
aaccagacca gtgggggagct gcgactcagc cgaaagctag acaataaccg cccactggtg 3720
gcctccatgt tggtgactgt cacagatggc ctgcacagcg tgacggcgca gtgtgtgctg 3780
cgcgtggtca tcatcacgga ggagttgctg gccaacagcc tgaccgtgcg ccttgagaac 3840
atgtggcagg agcgcttcct gtcaccgctg ctgggccgct tcctcgaggg cgtggctgcg 3900
gtgctcgcta cgcccgctga ggacgtcttc atcttcaaca tccagaacga cacagacgta 3960
gggggcaccg tgctcaatgt gagtttctcg gcgctagctc cacgtgggggc cggggcgggc 4020
gctgcagggc cctggttcag ctccgaggag ctgcaagagc agttgtacgt gcgccgggcg 4080
gcgctggcgg ctcgctccct gctcgacgta ctgcccttcg acgacaacgt gtgcctgcga 4140
gagccctgtg agaactacat gaaatgcgtg tccgtgctcc gctttgactc gtccgcgccc 4200
```

```
ttcctggcct cggcctccac gctgttccga cccatccagc ccatcgctgg cctgcgctgc 4260
cgctgcccgc ccggattcac gggagacttt tgcgagaccg agctcgacct ctgctactcc 4320
aacccatgtc gcaacggcgg agcctgcgcg cggcgcgagg gaggctacac gtgcgtctgc 4380
cgcccgcgct tcaccggaga ggactgcgag ctggacaccg aggccggccg ctgcgtgccg 4440
ggcgtctgcc gcaacggggg cacctgcacc gacgcgccca acggcggctt tcgctgccag 4500
tgcccggcag gcggcgcctt cgagggccgg cgctgcgagg tggctgcgcg ctccttcccg 4560
cccagttcgt tcgtcatgtt tcgcggcctg cggcagcgat tccaccttac gctgtccctc 4620
tcgttcgcga cagtgcagca gagcgggctg ctcttctaca acgggcgcct gaacgagaag 4680
cacgacttcc tggccctgga actcgtggct ggccaagtgc ggctcacata ttccacgggt 4740
gaatccaaca ccgtggtcag ccccacagtt ccaggggggct tgagtgacgg gcaatggcat 4800
acagtgcatc tgagatacta caacaagccc cggacagatg ccctagggggg tgcacagggc 4860
ccctccaagg acaaggtggc tgtgctaagc gtggatgatt gtgatgtggc cgtggctctg 4920
cagtttggtg ctgagattgg caactactca tgcgcggctg ctggtgtgca aacaagctcc 4980
aagaagtccc tggacctgac gggccctctt cttctgggag gtgtccccaa cctccccgag 5040
aacttccccg tatcccataa ggacttcatc ggctgtatgc gggacctgca cattgatggc 5100
cgccgagtgg acatggcggc ttttgtcgca aataatggca ccatggcagg ctgccaagcc 5160
aagctacact tttgtgactc aggcccctgc aagaacagtg gcttctgctc ggagcgctgg 5220
ggcagcttca gctgcgactg ccctgtgggc ttcggcggca aagactgtca gcttactatg 5280
gcccatcccc accatttccg tggcaacggc acactgagct ggaactttgg aagtgacatg 5340
gctgtgtctg tgccatggta cctgggggctg gcatttcgga cacgggcaac gcaggggggtc 5400
ctgatgcaag tgcaggctgg gccacacagc acgctcctttt gccagctaga tcggggggtta 5460
ctgtctgtga cagtgaccag gggctcgggc cgtgcttccc atctccttct ggaccaggtg 5520
actgtcagtg atggccggtg gcacgatctg cggctggagt tgcaggagga accaggtggc 5580
cggcggggcc accatgtcct tatggtctca ctggacttta gcctcttcca ggacaccatg 5640
gcggtgggga gtgagctgca gggcctgaag gtaaagcagc tccacgtggg aggcctgccc 5700
cccggcagtg cagaggaggc tcctcagggt ctggttggct gcatccagcc accgagtgaa 5760
tgcggacctg gctgtgttgt gaccaacgcc tgtgcctctg ggccctgccc acctcacgca 5820
gactgccggg acctcctggca gaccttttct tgcacctgcc agccaggtta ctacggccca 5880
ggctgtgtgg atgcctgcct cctgaacccc tgtcagaacc agggatcatg ccggcacctg 5940
ccaggagccc cccatggcta tacctgtgac tgtgtggggtg gctatttcgg gcaccactgt 6000
gagcacagga tggaccagca gtgcccacgg ggctggtggg ggagcccaac ctgtggcccc 6060
tgcaactgtg atgttcacaa aggttttgat cccaactgca acaagacaaa tgggcagtgt 6120
cactgcaagg agttccacta ccgaccgcgg ggcagtgact cttgcctccc atgtgactgc 6180
taccctgtgg gctccacctc gcgctcatgt gcaccccaca gcgggcagtg ccctgtcgc 6240
ccaggagccc ttggccgcca gtgcaacagc tgtgacagtc ccttcgcaga ggtgacagcc 6300
agcggctgcc gggtgctcta tgatgcctgc cctaagtccc tgagatctgg tgtgtggtgg 6360
ccccagacaa agtttggcgt cctggccaca gtgccctgtc cccggggggc cctgggattg 6420
cggggtgcag gtgctgctgt gcggctgtgt gatgaggccc agggttggct ggagcccgac 6480
ctcttcaact gtacctcccc tgcctttcga gagctcagtc tgctgctgga tggcctagag 6540
ctgaacaaga cggcactgga taccatggag gccaagaagc tggctcagcg gctacgggag 6600
gtgactggcc acactgacca ctattttagc caagatgttc gagtcactgc ccgcctgctg 6660
gcccacctgc tggccttcga gagccatcag cagggcttcg ggctgacagc cacacaggat 6720
gcccacttca atgagaatct gctgtgggcc ggctctgcac tgcttgcccc agagacaggg 6780
gacttgtggg cggcgctggg gcagcgggcc cctggggggct ccccaggcag cgcgggactg 6840
gtgaggcacc tggaggagta tgcagccaca ctcgcaagga atatggaact cacataccctg 6900
aatcccatgg ggctggtgac gcctaatatc atgctcagca ttgaccgcat ggagcacccc 6960
agttctcccc gggggggcccg tcgctaccct cgctaccata gcaacctctt tcgaggccag 7020
gatgcctggg atcctcacac ccatgtgctg ctgccttccc agtccccacg gccatcccca 7080
tctgaagttc tgcccacaag cagcagcata gaaaactcca ccacctcaag tgtggtcccc 7140
ccaccagccc cgccagagcc agagcctggg atctccatta tcattctcct cgtttaccgc 7200
accttagggg gactgctccc tgcccagttc caggcagaac gccgaggtgc caggcttcct 7260
cagaaccccg tcatgaactc cccggtggtc agcgtggctg tgttccacgg acgcaacttc 7320
ctaaggggaa tcctggagtc ccccatcagc ctagagtttc gcctgctaca gacagcgaat 7380
cggagcaagg cgatctgtgt gcagtgggac ccacctggcc tggcggagca gcatggtgtg 7440
tggacagcac gggactgcga gctggtgcac aggaatgggt cccacgcacg gtgtcgctgc 7500
agccggacag ggaccttggg ggtcctcatg gatgcctctc cccgtgagag gctggagggc 7560
gacctggagc tgctggctgt gttcacccac gtggtcgtgg ctgtgtctgt ggctgcgctg 7620
gtgctgactg cagccatcct gctgagcctg cgcagcctca gtccaatgt gcgtgggatc 7680
catgccaatg tggcagccgc cctgggggtg gcagagctcc tcttcctgct ggggattcac 7740
aggacccaca atcagctggt gtgcactgca gtcgccatcc tcctgcacta cttcttcctc 7800
agcaccttcg cgtggctctt cgtgcagggg ctgcacctct accgcatgca ggttgagcca 7860
cgcaacgtgg accgcgcgc catgcgcttc taccatgccc tgggctgggg cgtccctgct 7920
gtgctgctgg gccttgctgt gggcctggac cctgagggct atgggaaccc tgacttctgc 7980
tggatctcag tccacgagcc cctcatctgg agctttgctg ccctgttgt cctggtcata 8040
gtgatgaacg ggaccatgtt tctcctcgct gcccgcacat cctgctccac agggcagagg 8100
gaggccaaga gacctctgc actgaccctt cgcagctcct tcctgctgct tctgctggtc 8160
agtgcctcct ggctctttgg gctcctggca gtcaaccaca gcatcctagc cttccactac 8220
```

```
ctccatgctg gactctgcgg cctccagggc ctggcggtgc tgctgctctt ctgtgtccta 8280
aatgcagatg ctcgggctgc ctggatgcca gcctgtctgg gcaggaaggc agcgcctgag 8340
gaggcaaggc cagcacctgg gctgggacct ggggcctaca acaacacggc tctctttgag 8400
gagagtggcc tcatccgcat cactctgggc gcctccaccg tctcctctgt gagcagtgcc 8460
cgctccggcc ggacccagga ccaggacagc cagcggggcc gcagctacct cagggacaat 8520
gtcctggttc gacatggctc agccgctgac cacactgacc acagcctcca ggctcatgct 8580
ggccccactg acctggacgt ggccatgttc catcgagatg ctggcgcaga ctccgactct 8640
gacagtgacc tgtccttgga ggaggagagg agtctctcca ttccatcttc agaaagcgag 8700
gacaatggcc ggacgcgggg gcgcgtccaa cggccactct gccgagcagc ccagagtgag 8760
aggctcctca cccaccccaa agatgtggat ggcaatgacc tcctgtccta ctggccagcc 8820
ctggggggagt gcgaggcagc cccctgtgct ctgcagactt ggggctctga aaggcgcctg 8880
gggctggaca ccagcaagga tgcagctaac aacaaccagc cagacccggc cctgaccagt 8940
ggggatgaga cttctctggg ccgggcccag cgccagagga aaggcatcct gaagaaccgg 9000
ttgcaatacc cactggtgcc acagacccga ggtgccctg agctgtcctg gtgccgtgca 9060
gccaccttgg gccaccgtgc tgtgccagct gcctcttacg gtcgcatcta tgctggcggg 9120
ggcacgggca gcctttcaca gccagccagc cgctactctt ctagagaaca gctggacctg 9180
ctcctccggc ggcaactgag ccgtgagcga ctagaggaag ccctgcccc tgttctacgt 9240
cccctgagcc ggccagggtc ccaggaatgc atggatgctg caccaggccg actggagccc 9300
aaagatcggg gcagcaccct gccacggagg cagccacctc gggactaccc tggcgccatg 9360
gctggccgct tcgggtcacg ggatgcgctc gacttagggg cacctcgaga gtggttgagc 9420
acgctgcctc cgccccgccg cacccgggac cttgacccac agcccccacc tctgcccctg 9480
tctccccagc ggcaactctc aagggacccc ctcttgccat cccggccgct ggactctctg 9540
tctaggagct cgaactctcg ggagcagctg gaccaggtgc ctagccggca cccctcacga 9600
gaagcccttg ggccactccc gcagctgctc agagctaggg aggactcggt cagtggcccc 9660
agccatggcc cctccacaga acagttggac attctttcct ccatccttgc ctctttcaac 9720
tcctcggccc tctcctctgt gcaatcttca agcacaccct tgggccctca caccactgcc 9780
acaccttctg ccacagcctc tgtgcttggg ccctccacgc cacgttctgc cacgtctcac 9840
agcatctcgg agctgtcgcc agactcagaa gttcccagaa gtgagggtca ctcctgaggg 9900
gatgacggcg tggacgagga acagctgagg gcgacagagg atctaggcta acaggagaga 9960
ctccaggagt gggggcagat cccaaggcag cctcctgctc cccagtggtg ggtgccccag 10020
ctctacctgg tgtggcaggg ctgaggctcc atgtgcatct gtgagcatgc gtgtgacagg 10080
tgcagagacg ggggactgga gggagacttt tatacgtttt gtacctttgt aaccagagag 10140
atgcttatgt tattttctg ctttctgtc tcctggggctg tttgaggctg ggctgggagg 10200
gggagggaga tagagggaga gatgcagttt gaccccattt gggtcctgag caaaccctat 10260
gctcatctct ctctccttcc tggggtggac tcagatgggt gggacacatg ccttcctccc 10320
cctattccac ccccaagttg atctgagtat cgtcagggc ccaaagtaca gaattgttct 10380
ttgctttta ttgaatgctc caaaggccaa acttctgggg ctggggttg gtcttggaaa 10440
cagggtcct ctgacttcct catggggggct tgctcatacc gcccctcctg gtggatgtgt 10500
gtgtttatta tgtggagtcc ctgccactta ctgccttatg acctaggact gatgctgtgg 10560
ggtgctggtg gagcagctga tgtcgtgttt acagagcaag gcttccctgt ctcccacggg 10620
gaggggctcg ggcctctagt cagacattcc tgcagagggt cggtggaggg gtcattcacc 10680
tgcccctgca gcaagcaaaa gttgtctgtg gtgccatttg attccctgac actgcccct 10740
gcttgaattg attccgaagg gtagggtggg aaggtgagca aagggagcag aaacaaggga 10800
attcaagacc cagaatgtag gtgccactgc ctcctatgtt tacaggatcc tccgtggccc 10860
taggcacctg ggctgcagga agtgactccg ttccactcct cctttattcc cttaaaaagg 10920
gaaaaatgac tgttacgacc ctgttcacaa aactcttact tttgctattt tgtctgctgt 10980
ccagaactga agactttaaa attttgttac tgtttacaag tccagattca aaaaatgttt 11040
ttactttgtt tacaactcaa aactttgagt tttacacttt gtttacagta gataatttt 11100
tttcctttgt ttccaagtga aaggtaggga aagtgggaga gggacttgga ggacccacct 11160
gtgaggaccc tgacctggcc atcttgaggg gttttctaac ccccaggtct cccaggccga 11220
aggtcagcct tgagtccgt ttaacagcag atccagaaga ccttgagagt aggcgtcctc 11280
taaccacggg ggagagtggc tgtgcagggc tggggggtgg tctgtgcaga cacctcctca 11340
cccaccaccc catgcatact cttgggaagc agcttcctgg gagattagaa attctacttc 11400
cctgactgga gctaaatccc accagccagg acccaaactc tccttaccga gaaggacccc 11460
agctcttgaa gggctgagtg gcctgctggg ggtgggaggg tgtctttact atgtcctagg 11520
tttcgtagat gccctctct ggggttcccc tcctccagcc cagcggccct ctttcctgtc 11580
tgtgtaaatt gttccgtgaa gccgcgctct gttttgggaa taaacttcta tagaaaacaa 11640
aaaaaaaa                                                        11648
```